

## Redacted Data Submitted by the Primary Manufacturer and Other Interested Parties for Entresto

Below are redacted versions of the data submitted by the Primary Manufacturer and other interested parties in response to the Negotiation Program information collection request.<sup>1</sup> These redacted data have been redacted consistent with the confidentiality standards described in section 40.2 of the revised guidance and do not contain proprietary information, protected health information (PHI)/personally identifiable information (PII), or other information that is protected from disclosure under applicable law.

Respondents were permitted to include citations and attachments (hereinafter, collectively called “supplemental materials”) within their submissions for certain questions specified in the information collection request; therefore, you may observe that the number and order of any supplemental materials included as part of each response below will vary.

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<sup>1</sup> The Negotiation Program information collection request is available on the Office of Management and Budget’s (OMB’s) website at the following link: [https://www.reginfo.gov/public/do/PRAViewICR?ref\\_nbr=202306-0938-013](https://www.reginfo.gov/public/do/PRAViewICR?ref_nbr=202306-0938-013) and described in section 50 of revised guidance.

| Section 1194(e)(1) Data Factors   |
|---|
| <b>IPAY Year:</b> 2026  |
| <b>Manufacturer:</b> Novartis Pharms Corp   |
| <b>Drug:</b> Entresto (Valsartan/Sacubitrilat)  |
| <p><b>Background:</b> For the first year of the Medicare Drug Price Negotiation Program (“the Negotiation Program”), CMS selected 10 Part D high expenditure, single source drugs for negotiation. Section 1194(e) of the Act requires Centers for Medicare &amp; Medicaid Services (CMS) to consider two sets of factors as the basis for determining the offer and counteroffer throughout the negotiation process: (1) certain data that must be submitted by the manufacturer of each drug selected for negotiation and (2) evidence about alternative treatments, as available, with respect to each selected drug and therapeutic alternative(s) for each selected drug. After entering into an agreement under the Negotiation Program with CMS and in accordance with section 1193(a)(4) of the Act, the Primary Manufacturer of each selected drug submitted to CMS the following information with respect to a selected drug: information that CMS required to carry out negotiation, including but not limited to the factors listed in section 1194(e)(1) of the Act. For IPAY 2026, the Primary Manufacturer of each selected drug were tasked to provide the following data factors for each of its selected drug(s), which were specifically:</p> <ul style="list-style-type: none"> <li>C: Research and Development Costs and Recoupment,</li> <li>D: Current Unit Costs of Production and Distribution,</li> <li>E: Prior Federal Financial Support,</li> <li>F: Patents, Exclusivities, and Approvals, and</li> <li>G: Market Data and Revenue and Sales Volume Data.</li> </ul> <p>The Primary Manufacturer is responsible for aggregating and reporting all necessary data on its selected drug(s) from other parties, as applicable.</p> <p><b>Disclaimers:</b> With the exclusion of publicly available data, all manufacturer submitted data is considered proprietary and confidential. The data contained in this document are solely those of the authors and do not necessarily reflect the views or policies of CMS. The authors assume responsibility for the accuracy and completeness of the information contained in this document.</p> |

**Note:** Primary Manufacturers submitted required data in the Health Plan Management System (HPMS). Please note that the format of manufacturer responses is dependent on the data element requested. For example, some requested responses are “yes or no”, while other response options in HPMS provided a drop-down menu. However, some responses could be more complex and subjective, such as dollar



amounts, cost per unit, etc. For many questions, the ICR instructs the manufacturer to include an explanation. In some instances, an explanation is required and in other instances, the ICR directs the user to include an explanation “as necessary.” CMS instructs manufacturers to indicate “n/a” if they choose not to include an explanation in this case.

| C. Research and Development Cost  |   |   |  |  |   |   |   |
|---|---|---|--|--|---|---|---|
| <b>Description:</b> Section C contains five questions, related to different types of R&D costs incurred by the Primary Manufacturer, including acquisition costs. Each of these questions required the Primary Manufacturer to report, as applicable: (1) dollar amounts for R&D costs, which must be reported in the numerical response field and (2) explanations of how those costs were calculated in the free response field. Section C also contains one question about the Primary Manufacturer’s global and U.S. total lifetime net revenue for the selected drug. This question required the Primary Manufacturer to report, as applicable: (1) the dollar amount for global, total lifetime net revenue, which must be reported in the numerical response field, (2) an explanation of how this amount was calculated in the free response field, (3) the dollar amount for U.S. lifetime net revenue, which must be reported in the numerical response field, and (4) an explanation of how this amount was calculated in the free response field. |   |   |  |  |   |   |   |
| Primary Manufacturer Acquisition Costs of the Selected Drug   | Total Acquisition Costs for the Selected Drug | Basic Pre-Clinical Research for All Approved Indications of the Selected Drug | Post-IND Costs for All Approved Indications of the Selected Drug | Costs of Failed or Abandoned Products Related to the Selected Drug | Direct Costs of Other R&D for the Selected Drug Not Accounted for Above | Global Total Lifetime Net Revenue for the Selected Drug | U.S. Total Lifetime Net Revenue for the Selected Drug |
|   |   |   |  |  |   |   |   |

**Explanations:**

Explanation of Allocation of Total Acquisition Costs for the Selected Drug

None.

Explanation of Basic Pre-Clinical Research Costs

Novartis Pharmaceuticals Corporation (NPC) is submitting [REDACTED] in basic pre-clinical research and development (R&D) costs for Entresto® (sacubitril and valsartan), subject to the following parameters:

- The basic pre-clinical research period for Entresto is defined as January 22, 1992, through September 30, 2009, for both Entresto indications: treatment of adults with chronic heart failure (HF) and treatment of pediatric HF.
- [REDACTED]

The parameters, cost allocations, and calculations supporting this submission are described below.

## 1. ENTRESTO PRE-CLINICAL DEVELOPMENT

Entresto pre-clinical development is characterized by certain attributes unique to its status as a fixed-dose combination (FDC) product as well as the evolution of its potential use from a treatment for hypertension (HTN) to a treatment for HF. These pre-clinical efforts included several studies that extended beyond the active moiety and approved indications of Entresto, but nevertheless were appropriately submitted as part of the Entresto new drug application (NDA) under applicable federal standards. These efforts fall into two categories:

- Active moieties: Studies of sacubitril alone and sacubitril/valsartan combinations other than the complex approved as the active moiety in Entresto; and
- Approved indications: Studies of sacubitril and valsartan for the treatment of hypertension (HTN).

Where the results of such study efforts were included in the new drug application (NDA) submission for Entresto, consistent with federal guidelines, as discussed below, Novartis has included the costs of those efforts in the response to Question 2.

First, Entresto is an FDC product—and contains a complex of sacubitril and valsartan. [REDACTED]

[REDACTED] Consequently, the pre-clinical development of Entresto necessarily required R&D efforts in relation to sacubitril alone. FDA Guidance for Industry on the Nonclinical Safety Evaluation of Drug or Biologic Combinations specifies that each component of an FDC must be assessed independently for the potential for toxicity.<sup>1</sup> The Guide for the Care and Use of Laboratory Animals (The Guide), compulsory in the US by Public Health Service (PHS) policy, specifies that there should be no unnecessary duplication of experiments using animals.<sup>2</sup> Thus, relevant existing pre-clinical data on sacubitril alone and the administration of

a complex of sacubitril/valsartan were used to support the Entresto NDA for HF.

Second, the development of Entresto was initially focused on treatment for HTN, and pivoted to treatment for HF when already in the clinical phase. Rather than redo pre-clinical efforts tied to HTN, and consistent with FDA guidelines, Novartis relied on HTN-based pre-clinical study data for the Entresto NDA where appropriate. This approach is permitted, if not required by FDA Guidance to Industry on Good Clinical Practice, and National Institutes of Health (NIH) Guiding Principles for Ethical Research, which specify that the conduct of human clinical trials should not expose subjects to unnecessary risk and that the clinical study aims to increase scientific knowledge.<sup>3,4</sup> Therefore, whenever relevant human data are already available, they should be used to avoid unnecessary repetition of human studies. The efficacy of Entresto (LCZ696) was demonstrated in animal models of hypertension and heart failure using LCZ696, sacubitril (AHU377) or valsartan, confirming benefits on cardiac, renal, and vascular function.

The studies falling into these categories are identified below.

## 2. IDENTIFICATION OF R&D STUDIES INCLUDED IN QUANTIFYING REPORTED COSTS FOR ENTRESTO

Entresto is indicated:

- (1) To reduce the risk of cardiovascular death and hospitalization for HF in adult patients with chronic HF (benefits are most clearly evident in patients with left ventricular ejection fraction [LVEF] below normal) and
- (2) For the treatment of symptomatic HF with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older.

Direct and indirect costs for research related to the development of Entresto are included in the response to Question 2. For reasons previously cited, direct and indirect costs relating to certain research efforts involving the study of sacubitril alone and combinations of sacubitril/valsartan other than the complex approved as Entresto are included where the resulting research data were included in the Entresto NDA. As also discussed previously, in some cases research costs of these active moieties in relation to treatment for HTN are included, but only to the extent that the research data were included in the Entresto NDA.

[REDACTED]

[REDACTED]

[REDACTED]



[REDACTED]

[REDACTED]

These “project codes” are used to track direct expenditures. Code LCZ696 is the Development code for the complex of sacubitril and valsartan approved as Entresto. The project codes identified for inclusion in this response extend beyond LCZ696 for the reasons noted above.

[REDACTED]

- [REDACTED]
- LCZ696A: Development of LCZ696, the complex of sacubitril and valsartan approved as Entresto, for essential HTN. (Novartis included the costs of only those research and clinical studies used to support the FDA approval and thus only some of these costs were included.)
  - LCZ696B: Development of LCZ696 for HF with reduced ejection fraction (HFrEF). (All of these research costs were included.)
  - LCZ696D: Development of LCZ696 for HF with preserved ejection fraction (HFpEF). (All of these research costs were included.)

HFrEF and HFpEF are types of HF and thus of the FDA approved indications of Entresto.

3. THE BASIC PRE-CLINICAL RESEARCH PERIOD FOR ENTRESTO IS DEFINED AS JANUARY 22, 1992, THROUGH SEPTEMBER 30, 2009, FOR BOTH TREATMENT OF ADULTS WITH CHRONIC HF AND TREATMENT OF PEDIATRIC HF

The basic pre-clinical research period for both indications of Entresto is as follows:

- From January 22, 1992, the date on which the patent first describing sacubitril (AHU377) was filed, and thus the date by which it would be reasonable to assume that the neprilysin inhibitor used in Entresto had been invented or discovered.
- Through September 30, 2009, the day prior to the investigational new drug (IND) submission date of October 1, 2009, for HF, which applied to both the adult and pediatric indications of Entresto.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

#### REFERENCES

1. US Department of Health and Human Services, FDA, Center for Drug Evaluation and Research. Guidance for Industry: Nonclinical Safety Evaluation of Drug or Biologic Combinations. Mar. 2006. <https://www.fda.gov/media/119657/download>.



2. National Research Council of the National Academies. Guide for the Care and Use of Laboratory Animals. 8th ed. Washington D.C.: The National Academies Press; 2011. <https://doi.org/10.17226/12910>.

3. National Institutes of Health. NIH Clinical Research Trials and You: Guiding Principles for Ethical Research. Mar. 16, 2016. [NIH\\_guiding-principles-ethical-research](https://www.nih.gov/clinical-trials/guiding-principles-ethical-research).

4. FDA< E6(R3) Good Clinical Practice. May 19, 2023. <https://www.fda.gov/media/169090/download>.

#### Explanation of Post-IND Costs

Novartis Pharmaceuticals Corporation (NPC) is submitting [REDACTED] in post-investigational new drug (IND) research and development (R&D) costs in support of the development of Entresto® (sacubitril and valsartan) tablets, subject to the following parameters:

- The post-IND period for Entresto is defined as October 1, 2009, through February 8, 2023.
- Novartis has included costs for Phase 1, 2, and 3 clinical trials, as well as for any completed FDA-required post-approval research, including Phase 4 trials, in post-IND R&D costs.
- Only direct costs are included.
- Entresto received its FDA approval through the Priority Review approval pathway. FDA did not require any post-approval confirmatory studies for Entresto but did expect Novartis to complete certain post-approval commitment studies, the costs for which are included in Question 3.

[REDACTED]

The parameters, cost allocations, and calculations supporting this submission are described below.

#### 1. ENTRESTO'S POST-IND DEVELOPMENT

Entresto post-IND development is characterized by certain attributes unique to Entresto as a fixed-dose combination (FDC) product as well as the evolution of its potential use from a treatment for hypertension (HTN) to a treatment for heart failure (HF). Those post-IND efforts included

several studies that extended beyond the Entresto active moiety and approved indications, but nevertheless were appropriately submitted as part of the Entresto new drug application (NDA) under applicable federal standards. These efforts fall into two categories:

- Active moieties: Studies of sacubitril/valsartan combinations other than the complex approved as Entresto; and
- Approved indications: Studies of sacubitril and valsartan under a hypertension (HTN) IND.

Where the results of such study efforts were included in the NDA submission for Entresto, consistent with federal guidelines as discussed below, Novartis has included the costs of those efforts in the response to Question 3.

First, Entresto is an FDC product—a complex of sacubitril and valsartan. [REDACTED]

[REDACTED] That meant that the post-IND development of Entresto necessarily required R&D efforts in relation to sacubitril alone. FDA Guidance for Industry on the Nonclinical Safety Evaluation of Drug or Biologic Combinations specifies that each component of an FDC must be assessed independently for the potential for toxicity.<sup>1</sup> The Guide for the Care and Use of Laboratory Animals (The Guide), compulsory in the US by Public Health Service (PHS) policy, specifies that there should be no unnecessary duplication of experiments using animals.<sup>2</sup> Thus, relevant existing pre-clinical data on sacubitril alone and the administration of a complex of sacubitril/valsartan were used to support the Entresto NDA for HF.

Second, the development of Entresto was initially focused on treatment for HTN and studied under a HTN IND before pivoting to an HF IND, after which the clinical trial program went straight to Phase 3 by leveraging dose-finding studies of CLCZ696A2201 and CLCZ696A2223 in HTN, which supported the HF dose. Rather than redo clinical trials performed under the HTN IND, and consistent with FDA guidelines, Novartis relied on HTN IND clinical study data for the Entresto NDA where appropriate. This approach is permitted if not required by FDA Guidance to Industry on Good Clinical Practice, and National Institutes of Health (NIH) Guiding Principles for Ethical Research, which specify that the conduct of human clinical trials should not expose subjects to unnecessary risk and that the clinical study aims to increase scientific knowledge.<sup>3,4</sup> Therefore, whenever relevant human data are already available, they should be used to avoid unnecessary repetition of human studies. Thus, the Entresto NDA for HF relied on relevant existing data from clinical studies using Entresto in healthy volunteers or in subjects with HTN to support the safety evaluation and efficacious human dose selection.

These studies fall into the categories identified below.

## 2. IDENTIFICATION OF R&D STUDIES INCLUDED IN QUANTIFYING REPORTED COSTS FOR ENTRESTO

Entresto is indicated:

(1) To reduce the risk of cardiovascular death and hospitalization for HF in adults with chronic HF (benefits are most clearly evident in patients

with left ventricular ejection fraction [LVEF] below normal) and

(2) For the treatment of symptomatic HF with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older.

Direct costs for research related to the development of Entresto are included in the response to Question 3. For reasons cited previously, also included are direct costs relating to certain research efforts involving the study of combinations of sacubitril/valsartan other than the complex approved as Entresto, where the resulting research data were included in support of the Entresto NDA. As also discussed previously, in some cases research costs of these active moieties in relation to treatment for indications other than HF are included, but only to the extent the research data were included in the Entresto NDA.

[REDACTED]

[REDACTED]

Code LCZ696 is the Development code for the complex of sacubitril and valsartan approved as Entresto. The project codes identified for inclusion in this response extend beyond LCZ696 for the reasons noted previously.

The list of project codes for Biomedical Research and Development for which costs are included in the response to Question 3 are as follows:

- LCZ696A: Development of LCZ696, the complex of sacubitril and valsartan approved as Entresto, for essential HTN.
- LCZ696B: Development of LCZ696 for HF with reduced ejection fraction (HFrEF).
- LCZ696D: Development of LCZ696 for HF with preserved ejection fraction (HFpEF).
- LCZ696F: Development of LCZ696 for pediatric HF.

HFrEF, HFpEF, and pediatric HF are types of HF and thus of the FDA approved indications of Entresto and all followed from the same preclinical research.

[REDACTED]

3. THE POST-IND PERIOD FOR ENTRESTO IS DEFINED AS OCTOBER 1, 2009, THROUGH FEBRUARY 8, 2023



The post-IND research period for Entresto is defined as October 1, 2009, the date the IND went into effect for the first FDA-approved indication, through February 8, 2023, the date the last FDA required post-approval commitment trial was completed. Because FDA did not require Entresto to complete any post-approval confirmatory trials, Novartis has used the date the last post-approval commitment trial was completed as the end date for the post-IND period.

As noted above, Entresto was first studied in the clinical setting under an IND for HTN before pivoting to an HF IND, after which the clinical trial program proceeded directly to Phase 3. Rather than redo clinical trials performed under the HTN IND, and consistent with FDA guidelines, Novartis relied on HTN IND clinical study data for the Entresto NDA where appropriate. Thus, the response to Question 3 includes R&D costs for clinical trials performed under the Entresto IND for HTN, which went into effect on March 8th 2007, where the data from those trials were used in support of the Entresto NDA for HF.

#### 4. NOVARTIS HAS INCLUDED DIRECT COSTS FOR PHASE 1, 2, AND 3 CLINICAL TRIALS, AS WELL AS FOR COMPLETED FDA-REQUIRED POST-APPROVAL COMMITMENT RESEARCH, INCLUDING PHASE 4 TRIALS, IN POST-IND R&D COSTS

Novartis tracks clinical study costs for a given project code by building out the project code in two ways: first, the letter “C” is added to the beginning of the project code; second, a four-digit number is added to the end of the project code to identify the individual study. As a result, a clinical trial involving LCZ696A will be identified with a study code of CLCZ696A1101, for example. An overview of each of the project codes and their related clinical trials and costs is included below.

##### LCZ696A: Study of Entresto (LCZ696) for HTN

Entresto early clinical work in healthy volunteers and patients with HTN, Phase 1, began with a comprehensive HTN LCZ696A development program. The development plan included multiple food effect, drug-drug interaction (DDI), and pharmacokinetic and pharmacodynamic (PK/PD) studies. As stated in section 1, Entresto was first studied in the clinical setting under an IND for HTN before pivoting to an HF IND. Some of the research data from the IND for HTN were used in support of the NDA for HF.

LCZ696A Phase 2 clinical studies began with dose-ranging studies (in patients with HTN). Various special patient populations were included such as Asian, elderly, and people with renal- and hepatic-impairment. The pivotal dose-range-finding Phase 2 studies CLCZ696A2201 and CLCZ696A2223 were essential to further development of the HF program, which, with their inclusion in the NDA for Entresto, allowed Novartis to skip a Phase 2 dose-finding study for HF. Data gathered from these early studies were evaluated prior to commencing larger Phase 3 studies such as in the elderly HTN population (Study CLCZ696A2316) and the addition of amlodipine to LCZ696 (Study CLCZ696A2319). The HTN Phase 2 and Phase 3 studies were included in the HF dossier as they supported LCZ696 dosing and safety claims.

##### LCZ696B: Study of Entresto (LCZ696) for HFrEF

Early study data from the LCZ696A HTN program informed the decision to expand to the HF indication. The LCZ696B HFrEF clinical plan required further exploration of any DDI potential of LCZ696, effects in patients with renal impairment, and PK/PD in the HF patient population.

The HF program included a dose titration study in HF patients (Study CLCZ696B2228). The Phase 3 program included the large outcome study PARADIGM-HF (Study CLCZ696B2314) and its open-label extension study (Study LCZ696B2317), which provided evidence of LCZ696 clinical efficacy in patients with HFrEF. In addition, the PERSPECTIVE-HF study (CLCZ696B2320) was conducted to evaluate cognitive function as a post-approval commitment. A post-approval commitment study, requested and required by the FDA, was also completed (Study LCZ696B2013).

#### LCZ696D: Study of Entresto (LCZ696) for HFpEF

Novartis recognized the potential to expand the indication to include patients with HF with preserved Ejection Fraction (HFpEF), which was studied under the project code LCZ696D. Phase 2 and Phase 3 studies were conducted in support of the indication. Most notably, PARAMOUNT (Study CLCZ696D2214) provided therapeutic validation in an HFpEF population during Phase 2, PARAGON-HF (Study CLCZ696D2301) provided the key efficacy data to support this expanded indication, and PARALLAX (Study CLCZ696D2302) provided supportive efficacy and safety data during Phase 3.

#### LCZ696F: Study of Entresto (LCZ696) for pediatric HF

Lastly, as per FDA requirements, a clinical plan was developed for Entresto use in pediatric patients with HF (LCZ696F). This program required additional bioavailability studies and formulation development, as the pediatric population would not be able to use the current tablet formulation. Costs associated with the additional drug manufacturing along with PANORAMA-HF, the Phase 3 study (Study CLCZ696B2319) in pediatric patients and dossier submission, have been included. The open-label extension study to PANORAMA-HF (Study CLCZ696B2319E1) was not included as this is currently ongoing.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]



#### 6. ENTRESTO RECEIVED ITS FDA APPROVAL THROUGH THE PRIORITY REVIEW APPROVAL PATHWAY AND DID NOT NEED TO COMPLETE POST-APPROVAL CONFIRMATORY STUDIES

Entresto received its FDA approval through the Priority Review pathway and did not need to complete post-approval confirmatory studies. Novartis was required to complete post-approval commitment studies, including a standalone study CLCZ696B2320 (PERSPECTIVE), to evaluate the theoretical risk of long-term administration sacubitril/valsartan on cognitive function, and Study CLCZ696B2013, a non-interventional database study to estimate the incidence of serious angioedema among Black HF patients initiating LCZ696 (regardless of prior exposure to Angiotensin Converting Enzyme Inhibitors [ACEIs] or angiotensin receptor blocker [ARBs]) and among Black HF patients initiating ACEI treatment (treatment-naïve to ACEIs), separately. These costs were included in the response to Question 3.

[REDACTED]

[REDACTED]

#### REFERENCES

1. US Department of Health and Human Services, FDA, Center for Drug Evaluation and Research. Guidance for Industry: Nonclinical Safety Evaluation of Drug or Biologic Combinations. Mar. 2006. <https://www.fda.gov/media/119657/download>.
2. National Research Council of the National Academies. Guide for the Care and Use of Laboratory Animals. 8th ed. Washington D.C.: The National Academies Press; 2011. <https://doi.org/10.17226/12910>.
3. National Institutes of Health. NIH Clinical Research Trials and You: Guiding Principles for Ethical Research. Mar. 16, 2016. [NIH\\_guiding-principles-ethical-research](https://www.nih.gov/clinical-trials/guiding-principles-ethical-research).
4. FDA< E6(R3) Good Clinical Practice. May 19, 2023. <https://www.fda.gov/media/169090/download>.

Explanation of Costs on Allowable Failed or Abandoned Products Related to the Selected Drug

Novartis Pharmaceuticals Corporation (NPC) is submitting [REDACTED] in failed or abandoned product research and development (R&D) direct costs in support of the development of Entresto® (sacubitril and valsartan) tablets.

Entresto is a fixed-dose combination (FDC) of a neprilysin inhibitor or NEPi (sacubitril) and an angiotensin II receptor blocker or ARB (valsartan). Entresto inhibits neprilysin via LBQ657, the active metabolite of the prodrug sacubitril, and blocks the angiotensin II type-1 (AT1) receptor via valsartan. The cardiovascular and renal effects of Entresto in heart failure (HF) patients are attributed to the increased levels of peptides that are degraded by neprilysin, such as natriuretic peptides, and the simultaneous inhibition of the effects of angiotensin II by valsartan. Valsartan inhibits the effects of angiotensin II by selectively blocking the AT1 receptor and inhibiting angiotensin II-dependent aldosterone release.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

#### Explanation of Costs of Other R&D

Novartis Pharmaceuticals Corporation (NPC) is submitting [REDACTED] in other research and development (R&D) costs for Entresto® (sacubitril and valsartan), subject to the following parameters:

- The included R&D costs relate exclusively to the active moiety of Entresto for Food and Drug Administration (FDA)-approved indications.
- The included direct costs relate to:
  - Certain health economics & outcome research (HEOR) Studies;
  - Certain investigator-initiated trials (IITs); and
  - Certain Phase IV clinical trials.



The parameters, cost allocations, and calculations supporting this submission are described below.

1. R&D costs relate exclusively to the active moiety of Entresto for FDA-approved indications

Entresto is a fixed-dose combination (FDC) of sacubitril and valsartan and is indicated:

- (1) To reduce the risk of cardiovascular death and hospitalization for heart failure (HF) in adults with chronic HF (benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal) and
- (2) For the treatment of symptomatic HF with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older.

All costs included in this response to Question 5, Direct Costs for Other R&D, are direct costs specific to research involving Entresto for one or both of its labeled indications. There are three such categories of R&D costs for Entresto included herein:

- HEOR Studies
- IITs; and
- Phase IV Clinical Trials.

All costs included relate to completed studies or, in the case of ongoing studies, those costs incurred to date by NPC.

## 2. HEOR Studies

HEOR studies have played an important role in informing patients access to and clinical adoption of Entresto for treatment of chronic HF (CHF) in the US. Specifically, they have served three key purposes, with certain studies serving more than one:

- 1) Informing payer coverage decisions at the time of Entresto FDA approval for treatment of adults with HF and reduced ejection fraction (HFrEF) in 2015, as well as the launch of the expanded adult CHF indication in 2021, with respect to expected medical cost offsets and net payer budget impact of covering Entresto on formulary without restrictions beyond appropriate use as defined in the product label. These studies include CLCZ696BUS20, CLCZ696BUS21, CLCZ696BUS34 and health economic models of Entresto

- CLCZ696BUS20: Retrospective Study Refresh of Drug Utilization, Healthcare Resource Utilization, and Costs in Patients Treated with Entresto vs. ACE-I/ARB
- CLCZ696BUS21: Patient characteristics, treatment patterns, and healthcare resource utilization in patients with systolic HF and treated with Entresto compared with ACEI/ARB
- CLCZ696BUS34: Impact of Formulary Coverage of Entresto (Sacubitril/Valsartan) on Prescription Abandonment/Rejection and Subsequent Treatment and Economic Outcomes in CHF Patients in the US

2) Contextualizing clinical trial data with real-world experience of Entresto in HF patients in the US in terms of utilization patterns (e.g., utilization rate, patient adherence, and persistence) and real-world effectiveness of Entresto in reducing mortality and morbidity in diverse HF populations in routine clinical practice. These studies include CLCZ696BUS05, CLCZ696BUS16, CLCZ696BUS19, CLCZ696BUS27, and CLCZ696DUS07.

- CLCZ696BUS05: Observational Registry of Treatment Patterns in US HFrEF (CHAMP-HF)
- CLCZ696BUS16: An HF Analysis from the PINNACLE Registry
- CLCZ696BUS19: Clinical outcomes (real-world) Entresto vs. ACEi or ARB; This is an ongoing study. Only costs funded by Novartis for effort conducted by external entities to date are included in the submitted direct costs.
- CLCZ696BUS27: In-hospital Use of Sacubitril/Valsartan and Post-discharge Adherence and Clinical Outcomes Following Hospitalization for HFrEF.
- CLCZ696DUS07: Adoption of Novel HF Therapy and Outcomes in Patients with HF with Mildly Reduced or Preserved Ejection Fraction; This is an ongoing study. Only costs funded by Novartis for effort conducted by external entities to date are included in the submitted direct costs.

3) Complementing clinical trial data with evidence on effects of Entresto on improving patient-reported outcomes and reducing medical expenditures for HF patients in the US. These studies include CLCZ696BUS05, CLCZ696BUS17, CLCZ696BUS20, CLCZ696BUS21, CLCZ696BUS29, CLCZ696BUS34.

- CLCZ696BUS05: Observational Registry of Treatment Patterns in US HF Patients with HFrEF (CHAMP-HF)
- CLCZ696BUS17: PROVIDE-HF: Patient Reported Outcomes Investigation following Initiation of Drug Therapy with Entresto (Valsartan/Sacubitril) in HF
- CLCZ696BUS20: Retrospective Study Refresh of Drug Utilization, Healthcare Resource Utilization, and Costs in Patients Treated with Entresto vs. ACE-I/ARB

- CLCZ696BUS21: Patient characteristics, treatment patterns, healthcare resource utilization in patients with systolic HF and treated with Entresto compared with ACEI/ARB
- CLCZ696BUS29: Role of Sacubitril/Valsartan in Improving Provider Performance in Managing HF Spending under Medicare Alternative Payment Models
- CLCZ696BUS34: Impact of Formulary Coverage of Entresto (Sacubitril/Valsartan) on Prescription Abandonment/Rejection and Subsequent Treatment and Economic Outcomes in CHF Patients in the US

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]



### 3. INVESTIGATOR INITIATED TRIALS

IITs serve two key purposes:

1) IITs clarify the mechanisms of action (MoA), clinical benefits and safety, and effects on special patient populations, which, with respect to Entresto, included HF patients with co-morbid COVID-19, advanced heart failure, diabetes mellitus, pulmonary hypertension, and essential hypertension.

- CLCZ696BUS04T: Entresto™ (LCZ696) In Advanced Heart Failure (LIFE Study)
- LCZ696BUSNC03T: Role of LCZ696 in preventing the pathogenesis and progression of chronic kidney disease
- LCZ696BUSNC04T: LCZ696 is a Potential Direct Inhibitor of Fibrosis and Cardiac Remodeling
- LCZ696BUSNC06T: Beneficial mechanisms of the dual angiotensin receptor-neprilysin inhibitor LCZ696 for the treatment of heart failure
- LCZ696BUSNC07T: Cardiac, Renal and Liver Metabolic Effects of LCZ696, A Novel Angiotensin Receptor Neprilysin Inhibitor (ARNI)
- LCZ696BUSNC08T: LCZ696 in Pulmonary Hypertension and Right Ventricular Dysfunction
- LCZ696BUSNC11T: Effects of LCZ696 on cardiac function and remodeling response to chronic pressure overload
- LCZ696BUSNC13T: Anti-fibrotic mechanisms of Entresto™ in heart failure
- LCZ696BUSNC15T: Effects of LCZ696 on Myocardial Nitric Oxide and Hydrogen Sulfide Bioavailability in the Setting of Hypertension and Heart Failure
- LCZ696BUSNC16T: LCZ696 Prevents Pathological Vascular Remodeling
- LCZ696BUSNC18T: LCZ696 Increases Exosome Production to Restore the Peri-Infarct Region of the Injured Myocardium
- LCZ696BUSNC19T: Exploring the benefits of LCZ696 in pressure overload-induced heart failure and mechanisms by which dual neutral endopeptidase and angiotensin receptor inhibition with LCZ696 prevents pathologic cardiac remodeling
- LCZ696BUSNC20T: Ventricular Morphological and Mechanical Response to LCZ696
- CLCZ696BUS31T: Protecting with ARNI Against Cardiac Consequences of Coronavirus Disease 2019 (PARACOR-19). The PARACOR-19 trial, which is not yet final, is an examination of Entresto effects on patients with HF and co-morbid COVID-19. Last patient / last visit has already been conducted, and the trial is in final data analysis and manuscript preparation at this time. All included costs for this trial are those that have already been expended. All other IITs in this section are complete.

2) IITs further promote independent exploration of important topics related to the use of Entresto by accomplished and eminent physician scientists.

- CLCZ696BUS01T: Prospective comparison of an ARNI with an ACE inhibitor on endOthial function by brachial artery Reactivity (PARADOR)
- CLCZ696BUS02T: Demonstration of Reverse Remodeling Effects of Entresto™ (valsartan/sacubitril) Using Echocardiography Endocardial Surface Analysis (REMODEL-HF)
- CLCZ696BUS03T: Pulmonary Artery Pressure Reduction with ENTresto (sacubitril/valsartan) - PARENT Trial
- LCZ696BUSNC01T: Effects of Chronic Therapy with LCZ696 on Long-term Outcomes in Dogs with Experimentally-Induced Cardiorenal Syndrome
- LCZ696BUSNC02T: LCZ696 for Cardio-Renal Protection in a Translational Rabbit Model of HFrEF
- LCZ696BUSNC05T: Heart failure therapy with LCZ696 in rat models of pressure- and volume-overload
- LCZ696BUSNC09T: Effect of LCZ696 on Insulin Secretion and Glucose Homeostasis
- LCZ696BUSNC10T: Effect of LCZ696 on Diabetic Vascular and Neural Complications
- LCZ696BUSNC12T: Impact of Dual Acting Angiotensin-Receptor/Neprilysin Inhibitor (ARNi) Therapy on Abnormal Cardiac, Vascular and Renal Function in Male Zucker Rats
- LCZ696BUSNC14T: LCZ696 in preclinical models of diabetic cardiomyopathy and vasculopathy
- LCZ696BUSNC17T: MMP targeted imaging in early detection and future prediction of chemotherapy induced cardiotoxicity
- LCZ696BUSNC21T: Impact of LCZ696 on in vivo and in vitro chronic Angiotensin II-pressure overload-induced cardiomyopathy in mice
- LCZ696BUSNC22T: Effects of LCZ696 on myocardial remodeling, hemodynamic function and mitochondrial energetics in mice with metabolic syndrome

[REDACTED]

[REDACTED]



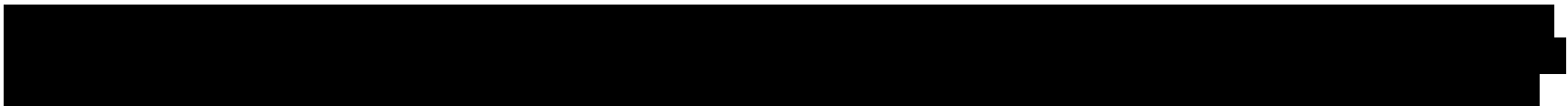
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#### 4. Phase 4 clinical trials

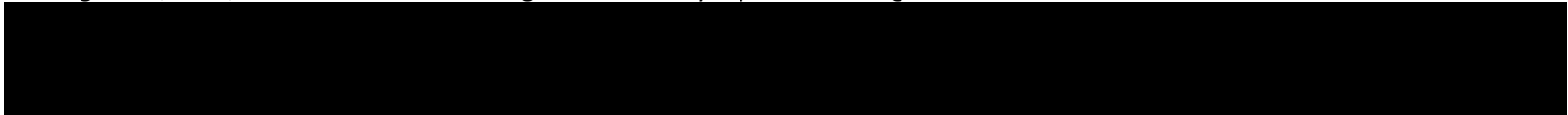
Ph 4 clinical trials were conducted to further clarify the MoA, clinical benefits and safety, and effects on special patient populations of Entresto in the US. These trials include:

- AWAKE-HF (CLCZ696BUS14): a prospective study of Entresto treatment effects on sleep disordered breathing in patients with HF, which is a highly prevalent comorbidity
  - PIONEER-HF (CLCZ696BUS01): a prospective study of stabilized acute HF patients hospitalized and shortly after hospitalization treated with Entresto versus ACEi. This study was significant for having been conducted exclusively in the United States and including a very large proportion of self-reported black subjects (36%). The study answered the question of feasibility, safety and efficacy for initiating Entresto in hospital, very shortly after stabilization of an acute exacerbation event.
  - PROVE-HF (CLCZ696BUS13): a prospective single-arm study of patients with HFrEF, measuring the cardiac structural and functional improvements associated with improvements in the biomarker, NT-proBNP following treatment with Entresto.
  - EVALUATE-HF (CLCZ696BUS08): a study of the effect of Entresto on aortic stiffness as a potential explanation for pathophysiological mechanism contribution to HF clinical outcomes
  - PARAGLIDE-HF (CLCZ696DUS01): was the most recent and final planned Phase 4 trial that examined the clinical effects of Entresto on patients with HF and preserved ejection fraction (HFpEF) in the setting of a worsening HF event or HF hospitalization.
- 
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- 



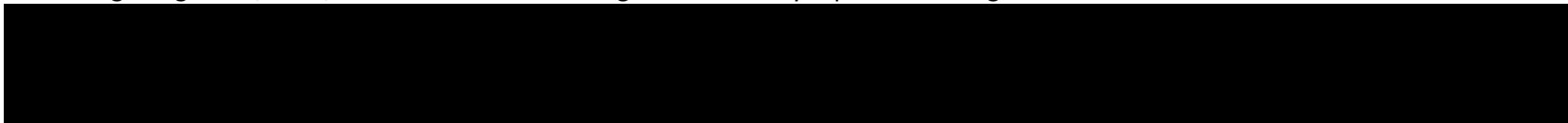
#### Explanation of Global Lifetime Net Revenue

- Global, net revenue since launch of July 2015 through most recent publicly reported earnings of June 2023. Data is not available through August 29, 2023, and therefore data through most recently reported earnings statement used.

- 
- Net revenue defined as direct sales, less discounts, chargebacks, rebates, cash discounts, free goods contingent on a purchase agreement, up-front payments, coupons, or other price concessions.

#### Explanation of U.S. Lifetime Net Revenue

- US, net revenue since launch of July 2015 through the most recent publicly reported earnings of June 2023. Data is not available through August 29, 2023, and therefore data through most recently reported earnings statement used.

- 
- Net revenue defined as direct sales, less discounts, chargebacks, rebates, cash discounts, free goods contingent on a purchase agreement, up-front payments, coupons, or other price concessions.

#### D. Current Unit Costs of Production and Distribution

**Background:** Manufacturers were required to report production and distribution unit costs separately for each NDC-11 of the selected drug, including any NDC-11 of the selected drug marketed by a Secondary Manufacturer. A free response field was provided to explain the methodology for calculating the amount reported.

| NDC-11        | Average Per Unit<br>Production Cost | Average<br>Per Unit<br>Distribution<br>Costs | Indicate Unit<br>Used | Total Unit Volume |
|---------------|-------------------------------------|--|-----------------------|-------------------|
| 00078-0659-20 |                                     |  | EA                    |                   |
| 00078-0659-67 |                                     |  | EA                    |                   |
| 00078-0696-20 |                                     |  | EA                    |                   |
| 00078-0696-67 |                                     |  | EA                    |                   |
| 00078-0777-20 |                                     |  | EA                    |                   |
| 00078-0777-67 |                                     |  | EA                    |                   |

#### Explanations:

- Average unit cost during the 12-month period ending May 31, 2023
- Local total production costs include transfer pricing, labor, freight and insurance
- Local total production cost (primarily transfer price) per unit, only applicable on US sold units with no ex-US costs. There are no further allocated shared operating or other indirect costs to include.
- Excludes R&D and marketing costs
- Local distribution costs include costs for physical storage, related IT management and indirect staff, freight out, utilities, internal pick and pack operations and supplies.
- Calculation considers total Entresto unit volumes (excluding free goods) divided by total US sold unit volumes to determine a reasonable allocation for variable effort and related costs.
- Free goods were excluded from unit volume, on the assumption that such goods do not constitute U.S. sales, but included in costs. This is because Novartis is able to isolate and exclude free good units from sales volume but cannot isolate and exclude costs for producing and distributing those units.





| E. Federal Financial Support   |                           |                   |  |                      |
|--|---------------------------|-------------------|--|----------------------|
| <b>Description:</b> This section pertains to all prior federal financial support provided by federal agencies or federally supported grants or contracts that contributed to direct costs for the basic pre-clinical research and clinical trials phase of research and development for FDA-approved indications of the selected drug to the Primary Manufacturer only. It also pertains to prior federal financial support received for indirect costs of developing the selected drug. |                           |                   |  |                      |
| Total Federal Financial Support  | Federal Financial Support | Type of Agreement | Federal Agency(ies) Participating in Agreement | Nature of Agreement  |
| \$0.00   | not applicable (N/A)      | OTH               | not applicable (N/A)                           | not applicable (N/A) |

Explanations: None.

## F. Patents, Exclusivities, and Approvals

### Patents (Expired and Non-Expired) and Patent Applications

**Description:** Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. This table lists each patent that is related to the selected drug, as well as each application for a patent related to the selected drug that is pending with the USPTO.

| Patent #  | Date Filed | Patent Expiry Date | Drug Product Patent | Drug Substance Patent | Drug Method of Use Patent | Patent Application Pending | Patent Type | Listed in FDA Orange Book / Purple Book |
|-----------|------------|--------------------|---------------------|-----------------------|---------------------------|----------------------------|-------------|---|
| 5217996   | 1992-01-22 | 1997-06-08         | Y                   | Y                     | Y                         | N                          | UTL         | N                                       |
| 5399578   | 1992-12-29 | 2012-03-21         | Y                   | Y                     | Y                         | N                          | UTL         | N                                       |
| 6294197   | 1997-06-18 | 2017-06-18         | Y                   | N                     | Y                         | N                          | UTL         | N                                       |
| 7468390   | 2003-01-14 | 2023-11-27         | Y                   | N                     | N                         | N                          | UTL         | Y                                       |
| 8101659   | 2008-06-27 | 2025-01-15         | Y                   | N                     | N                         | N                          | UTL         | Y                                       |
| 8404744   | 2011-12-16 | 2023-01-14         | Y                   | N                     | N                         | N                          | UTL         | Y                                       |
| 8796331   | 2012-11-28 | 2023-01-14         | N                   | N                     | Y                         | N                          | UTL         | Y                                       |
| 8877938   | 2006-11-08 | 2027-05-27         | Y                   | Y                     | N                         | N                          | UTL         | Y                                       |
| 9388134   | 2014-06-23 | 2026-11-08         | N                   | N                     | Y                         | N                          | UTL         | Y                                       |
| 9517226   | 2013-08-22 | 2033-08-22         | N                   | N                     | Y                         | N                          | UTL         | Y                                       |
| 9937143   | 2016-11-08 | 2033-08-22         | N                   | N                     | Y                         | N                          | UTL         | Y                                       |
| 10596151  | 2018-02-27 | 2036-08-24         | N                   | N                     | Y                         | N                          | UTL         | N                                       |
| 10722471  | 2018-08-01 | 2037-02-02         | Y                   | N                     | Y                         | N                          | UTL         | N                                       |
| 11058667  | 2017-11-07 | 2036-05-09         | N                   | N                     | Y                         | N                          | UTL         | Y                                       |
| 11096918  | 2019-09-23 | 2026-11-08         | Y                   | Y                     | N                         | N                          | UTL         | N                                       |
| 11135192  | 2018-03-06 | 2033-08-22         | N                   | N                     | Y                         | N                          | UTL         | Y                                       |
| 11642329  | 2022-06-23 | 2026-11-08         | Y                   | Y                     | N                         | N                          | UTL         | N                                       |
|           |            |                    |                     |                       |                           |                            |             |   |
| 18/364880 | 2023-08-03 | 2037-02-02         | N                   | N                     | Y                         | Y                          | UTL         | N                                       |



## F. Patents, Exclusivities, and Approvals

### Patents (Expired and Non-Expired) and Patent Applications

**Description:** Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. This table lists each patent that is related to the selected drug, as well as each application for a patent related to the selected drug that is pending with the USPTO.

| Patent #  | Date Filed | Patent Expiry Date | Drug Product Patent | Drug Substance Patent | Drug Method of Use Patent | Patent Application Pending | Patent Type | Listed in FDA Orange Book / Purple Book |
|-----------|------------|--------------------|---------------------|-----------------------|---------------------------|----------------------------|-------------|---|
| 17/103327 | 2020-11-24 | 2034-08-26         | N                   | N                     | Y                         | Y                          | UTL         | N                                       |
| 17/371585 | 2021-07-09 | 2036-05-09         | N                   | N                     | Y                         | Y                          | UTL         | N                                       |
| 17/395305 | 2021-08-05 | 2026-11-08         | Y                   | Y                     | N                         | Y                          | UTL         | N                                       |
| 18/353522 | 2023-07-23 | 2033-08-22         | N                   | N                     | Y                         | Y                          | UTL         | N                                       |
| 18/314745 | 2023-05-09 | 2028-11-04         | N                   | N                     | Y                         | Y                          | UTL         | N                                       |

**Explanations:** US Patent Nos. 7468390 and 8101659 are listed in the Orange Book for Entresto and cover, for example, pharmaceutical compositions including a combination of valsartan or a pharmaceutically acceptable salt thereof and sacubitril or a pharmaceutically acceptable salt thereof. They expire in November 2023 (including Patent Term Adjustment or PTA) and January 2025 (including Patent Term Extension or PTE), respectively. Pediatric exclusivity associated with these patents expires in May 2024 and July 2025, respectively. Two additional patents from the same family were listed in the Orange Book for Entresto and expired in January 2023 - US Patent Nos. 8404744 and 8796331. These patents also cover, for example, pharmaceutical compositions including combinations of valsartan or a pharmaceutically acceptable salt thereof and sacubitril or a pharmaceutically acceptable salt thereof and methods of treating hypertension or heart failure with such compositions.

US Patent Nos. 8877938 and 9388134 are listed in the Orange Book for Entresto and cover, for example, crystalline complexes of valsartan and sacubitril. They expire in May 2027 (including Patent Term Adjustment or PTA) and November 2026, respectively. Pediatric exclusivity associated with these patents expires in November 2027 and May 2027, respectively. Two additional patents from the same family are not listed in the Orange Book and cover, for example, an amorphous form of valsartan and sacubitril – US Patent Nos. 11096918 and 11642329. They expire in November 2026. There is one additional pending patent application in this family – Serial No. 17/395,305.

US Patent Nos. 9517226, 9937143, and 11135192 are listed in the Orange Book for Entresto and cover, for example, methods of treating heart failure with preserved ejection fraction (HFpEF) in a human patient by administering a combination of valsartan or a pharmaceutically acceptable

salt thereof and sacubitril or a pharmaceutically acceptable salt thereof. These patents relate to the expanded Entresto indication in chronic heart failure approved in February 2021 based on efficacy and safety observed in the PARAGON-HF clinical trial. They expire in August 2033. There is one additional pending patent application in this family – Serial No. 18/353,522.

US Patent No. 11058667 is listed in the Orange Book for Entresto and covers, for example, a dosage regimen for treating chronic heart failure with reduced ejection fraction (HFrEF) in a patient neither taking an angiotensin-converting enzyme (ACE) inhibitor nor an angiotensin II receptor blocker (ARB) or only taking a low dose of such agents before initiating treatment with sacubitril and valsartan. This patent relates to the TITRATION-HF clinical trial and Section 2.5 of the Entresto label. It expires in May 2036. There is one additional pending patent application in this family – Serial No. 17/371,585.

US Patent No. 10722471 covers, for example, a minitabket formulation including sacubitril and valsartan for use in pediatric patients. This formulation is the subject of NDA 218591 filed in June 2023. It is not yet approved by FDA and thus the patent is not listed in the Orange Book. This application relates to the PANORAMA-HF clinical trial and methods for treating heart failure in pediatric patients.

US Patent Nos. 5217996 and 5399578 cover, for example, the sacubitril compound and valsartan compound, the two pharmacologically active components of Entresto, respectively. They are both expired.

US Patent No. 6294197 covers, for example, solid oral dosage forms including valsartan, one of the two pharmacologically active components of Entresto, and is expired. This patent was listed in the Orange Book for Diovan, Diovan HCT, Exforge, and Exforge HCT.

US Patent No. 10596151 covers, for example, methods of reducing arterial stiffness in a patient with hypertension by administering a combination of sacubitril and valsartan. Entresto is not approved in the US to treat hypertension and thus this patent is not listed in the Orange Book. This patent relates to the PARAMETER clinical trial.

US Application Serial No. 18/364,880 is pending and relates to methods for treating heart failure in a human pediatric patient by administering combinations of sacubitril and valsartan.

US Application Serial No. 17/103,327 is pending and relates to methods for reducing a risk of cardiovascular death and hospitalization compared to that from enalapril in a patient with chronic heart failure and reduced ejection fraction (HFrEF) by administering combinations of sacubitril and valsartan. This application relates to the PARADIGM-HF clinical trial.

US Application Serial No. 18/314,745 is pending and relates to tablet formulations of sacubitril and valsartan, including the Entresto tablet formulation, and methods of treating a cardiovascular condition or disease with such formulations.

| F. Patents, Exclusivities, and Approvals   |                             |                              |  |   |
|--|-----------------------------|------------------------------|--|---|
| Regulatory Exclusivity Periods   |                             |                              |  |   |
| <b>Description:</b> Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. Manufacturers reported all regulatory exclusivity periods under the FD&C Act or the PHS Act that are listed in the Orange Book or the Purple Book and in effect or have expired for the selected drug. |                             |                              |  |   |
| Type of Exclusivity  | Exclusivity Expiration Date | Application (NDA/BLA) Number | NDC-9s Covered by Exclusivity                              | Comments  |
| CIE  | 2024-02-16                  | 207620                       | 00078-0659; 00078-0696; 00078-0777; 00078-9659; 00078-9777 | M-82 (Labeling revisions related to clinical studies i.e. PARAGON-HF) |
| PED  | 2023-07-14                  | 207620                       | 00078-0659; 00078-0696; 00078-0777; 00078-9659; 00078-9777 | US Patent No. 8404744   |
| PED  | 2023-07-14                  | 207620                       | 00078-0659; 00078-0696; 00078-0777; 00078-9659; 00078-9777 | US Patent No. 8796331   |
| PED  | 2024-05-27                  | 207620                       | 00078-0659; 00078-0696; 00078-0777; 00078-9659; 00078-9777 | US Patent No. 7468390   |
| PED  | 2025-07-15                  | 207620                       | 00078-0659; 00078-0696; 00078-0777; 00078-9659; 00078-9777 | US Patent No. 8101659   |
| PED  | 2027-11-27                  | 207620                       | 00078-0659; 00078-0696; 00078-0777; 00078-9659; 00078-9777 | US Patent No. 8877938   |



## F. Patents, Exclusivities, and Approvals

### Regulatory Exclusivity Periods

**Description:** Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. Manufacturers reported all regulatory exclusivity periods under the FD&C Act or the PHS Act that are listed in the Orange Book or the Purple Book and in effect or have expired for the selected drug.

| Type of Exclusivity | Exclusivity Expiration Date | Application (NDA/BLA) Number | NDC-9s Covered by Exclusivity                              | Comments  |
|---------------------|-----------------------------|------------------------------|--|---|
| PED                 | 2027-05-08                  | 207620                       | 00078-0659; 00078-0696; 00078-0777; 00078-9659; 00078-9777 | US Patent No. 9388134   |
| CEE                 | 2020-07-07                  | 207620                       | 00078-0659; 00078-0696; 00078-0777; 00078-9659; 00078-9777 |   |
| PED                 | 2021-01-07                  | 207620                       | 00078-0659; 00078-0696; 00078-0777; 00078-9659; 00078-9777 | New Chemical Entity Exclusivity                                       |
| CIE                 | 2022-10-01                  | 207620                       | 00078-0659; 00078-0696; 00078-0777; 00078-9659; 00078-9777 | New Patient Population (pediatric)                                    |
| PED                 | 2023-04-01                  | 207620                       | 00078-0659; 00078-0696; 00078-0777; 00078-9659; 00078-9777 | New Clinical Investigation Exclusivity (pediatric patient population) |

**Explanations:** None.

## F. Patents, Exclusivities, and Approvals

### All Active and Pending FDA Applications and Approvals

**Description:** Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. This list contains all active and pending FDA applications and approvals for the selected drug under section 505(c) of the FD&C Act and 351(a) of the PHS Act.

| Application (NDA / BLA) Number | Application Type (NDA; BLA) | Class Code | Approval Date | Indication   | Dosage Form and Strength                | Sponsor  | Application Status | Comments  |
|--------------------------------|-----------------------------|------------|---------------|--|---|----------|--------------------|---|
| 207620                         | NDA                         | 1          | 2015-07-07    | To reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction   | Film-coated tablets 50 mg/100 mg/200 mg | Novartis | APP                | Initial NDA for patients with heart failure and reduced ejection fraction (HFrEF).      |
| 207620                         | NDA                         | 1          | 2019-10-01    | 1) to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction 2) For the treatment of heart failure due to systemic left ventricular systolic dysfunction in pediatric | Film-coated tablets 50 mg/100 mg/200 mg | Novartis | APP                | Efficacy supplement to provide interim analysis data from the pediatric clinical study. |

## F. Patents, Exclusivities, and Approvals

### All Active and Pending FDA Applications and Approvals

**Description:** Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. This list contains all active and pending FDA applications and approvals for the selected drug under section 505(c) of the FD&C Act and 351(a) of the PHS Act.

| Application (NDA / BLA) Number | Application Type (NDA; BLA) | Class Code | Approval Date | Indication  | Dosage Form and Strength                | Sponsor  | Application Status | Comments   |
|--------------------------------|-----------------------------|------------|---------------|---|---|----------|--------------------|--|
|                                |                             |            |               | patients aged one year and older  |   |          |                    |  |
| 207620                         | NDA                         | 1          | 2021-02-16    | 1) to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure. Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal. LVEF is a variable measure, so use clinical judgement in deciding whom to treat 2) For the treatment of heart failure due to systemic left ventricular systolic dysfunction in pediatric | Film-coated tablets 50 mg/100 mg/200 mg | Novartis | APP                | Efficacy supplement to support use in patients with heart failure and preserved ejection fraction (HFpEF). |



## F. Patents, Exclusivities, and Approvals

### All Active and Pending FDA Applications and Approvals

**Description:** Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. This list contains all active and pending FDA applications and approvals for the selected drug under section 505(c) of the FD&C Act and 351(a) of the PHS Act.

| Application (NDA / BLA) Number | Application Type (NDA; BLA) | Class Code | Approval Date | Indication  | Dosage Form and Strength                 | Sponsor  | Application Status | Comments  |
|--------------------------------|-----------------------------|------------|---------------|---|--|----------|--------------------|---|
|                                |                             |            |               | patients aged one year and older  |  |          |                    |   |
| 207620                         | NDA                         | 1          |               | 1) to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure. Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal. LVEF is a variable measure, so use clinical judgement in deciding whom to treat 2) For the treatment of heart failure due to systemic left ventricular systolic dysfunction in pediatric | Film-coated tablets, 50 mg/100 mg/200 mg | Novartis | PEN                | This efficacy supplement satisfies an FDA request to submit the final results of the pediatric clinical study to allow for the label to include a summary of the full results. No change in indication is proposed. This supplement was submitted simultaneously with NDA 218591. Submitted on 14-Jun-2023. |

## F. Patents, Exclusivities, and Approvals

### All Active and Pending FDA Applications and Approvals

**Description:** Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. This list contains all active and pending FDA applications and approvals for the selected drug under section 505(c) of the FD&C Act and 351(a) of the PHS Act.

| Application (NDA / BLA) Number | Application Type (NDA; BLA) | Class Code | Approval Date | Indication  | Dosage Form and Strength                | Sponsor  | Application Status | Comments  |
|--------------------------------|-----------------------------|------------|---------------|---|---|----------|--------------------|---|
|                                |                             |            |               | patients aged one year and older  |   |          |                    |   |
| 218591                         | NDA                         | 3          |               | 1) to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure. Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal. LVEF is a variable measure, so use clinical judgement in deciding whom to treat 2) For the treatment of heart failure due to systemic left ventricular systolic dysfunction in pediatric | Film-coated granules, 12.5 mg/31.2 5 mg | Novartis | PEN                | This NDA is to introduce the film-coated granules for pediatric use. It cross-references NDA 207620, which contains the clinical data supporting the pediatric indication that was approved in 2019 and was supplemented in June 2023. No change to the labeled indication is proposed. Submitted on 14-Jun-2023. |

### F. Patents, Exclusivities, and Approvals

#### All Active and Pending FDA Applications and Approvals

**Description:** Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. This list contains all active and pending FDA applications and approvals for the selected drug under section 505(c) of the FD&C Act and 351(a) of the PHS Act.

| Application (NDA / BLA) Number | Application Type (NDA; BLA) | Class Code | Approval Date | Indication                       | Dosage Form and Strength | Sponsor | Application Status | Comments |
|--------------------------------|-----------------------------|------------|---------------|----------------------------------|--------------------------|---------|--------------------|----------|
|                                |                             |            |               | patients aged one year and older |                          |         |                    |          |

Explanations: None.

### G. Market Data and Revenue and Sales Volume Data

#### Wholesale Acquisition Cost Unit Price

**Description:** The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Wholesale Acquisition Cost (WAC) unit price of the selected drug.

| National Drug Code (NDC-11) | Quarter | WAC    | Unit type (each, ML, GM) | Total Unit Volume |
|-----------------------------|---------|--------|--------------------------|-------------------|
| 00078-0659-61               | 2018-Q3 | \$0.00 | EA                       |                   |
| 00078-0659-61               | 2018-Q4 | \$0.00 | EA                       |                   |
| 00078-0659-61               | 2019-Q1 | \$0.00 | EA                       |                   |



**G. Market Data and Revenue and Sales Volume Data**

**Wholesale Acquisition Cost Unit Price**

**Description:** The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Wholesale Acquisition Cost (WAC) unit price of the selected drug.

| National Drug Code (NDC-11) | Quarter | WAC    | Unit type (each, ML, GM) | Total Unit Volume |
|-----------------------------|---------|--------|--------------------------|-------------------|
| 00078-0659-61               | 2019-Q2 | \$0.00 | EA                       |                   |
| 00078-0659-61               | 2019-Q3 | \$0.00 | EA                       |                   |
| 00078-0659-61               | 2019-Q4 | \$0.00 | EA                       |                   |
| 00078-0659-61               | 2020-Q1 | \$0.00 | EA                       |                   |
| 00078-0659-61               | 2020-Q2 | \$0.00 | EA                       |                   |
| 00078-0659-61               | 2020-Q3 | \$0.00 | EA                       |                   |
| 00078-0659-61               | 2020-Q4 | \$0.00 | EA                       |                   |
| 00078-0659-61               | 2021-Q1 | \$0.00 | EA                       |                   |
| 00078-0659-61               | 2021-Q2 | \$0.00 | EA                       |                   |
| 00078-0659-61               | 2021-Q3 | \$0.00 | EA                       |                   |
| 00078-0659-61               | 2021-Q4 | \$0.00 | EA                       |                   |
| 00078-0659-61               | 2022-Q1 | \$0.00 | EA                       |                   |
| 00078-0659-61               | 2022-Q2 | \$0.00 | EA                       |                   |
| 00078-0659-61               | 2022-Q3 | \$0.00 | EA                       |                   |
| 00078-0659-61               | 2022-Q4 | \$0.00 | EA                       |                   |
| 00078-0659-61               | 2023-Q1 | \$0.00 | EA                       |                   |
| 00078-0659-61               | 2023-Q2 | \$0.00 | EA                       |                   |
| 00078-0659-35               | 2018-Q3 | \$0.00 | EA                       |                   |
| 00078-0659-35               | 2018-Q4 | \$0.00 | EA                       |                   |
| 00078-0659-35               | 2019-Q1 | \$0.00 | EA                       |                   |
| 00078-0659-35               | 2019-Q2 | \$0.00 | EA                       |                   |
| 00078-0659-35               | 2019-Q3 | \$0.00 | EA                       |                   |

**G. Market Data and Revenue and Sales Volume Data**

**Wholesale Acquisition Cost Unit Price**

**Description:** The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Wholesale Acquisition Cost (WAC) unit price of the selected drug.

| National Drug Code (NDC-11) | Quarter | WAC    | Unit type (each, ML, GM) | Total Unit Volume |
|-----------------------------|---------|--------|--------------------------|-------------------|
| 00078-0659-35               | 2019-Q4 | \$0.00 | EA                       |                   |
| 00078-0659-35               | 2020-Q1 | \$0.00 | EA                       |                   |
| 00078-0659-35               | 2020-Q2 | \$0.00 | EA                       |                   |
| 00078-0659-35               | 2020-Q3 | \$0.00 | EA                       |                   |
| 00078-0659-35               | 2020-Q4 | \$0.00 | EA                       |                   |
| 00078-0659-35               | 2021-Q1 | \$0.00 | EA                       |                   |
| 00078-0659-35               | 2021-Q2 | \$0.00 | EA                       |                   |
| 00078-0659-35               | 2021-Q3 | \$0.00 | EA                       |                   |
| 00078-0659-35               | 2021-Q4 | \$0.00 | EA                       |                   |
| 00078-0659-35               | 2022-Q1 | \$0.00 | EA                       |                   |
| 00078-0659-35               | 2022-Q2 | \$0.00 | EA                       |                   |
| 00078-0659-35               | 2022-Q3 | \$0.00 | EA                       |                   |
| 00078-0659-35               | 2022-Q4 | \$0.00 | EA                       |                   |
| 00078-0659-35               | 2023-Q1 | \$0.00 | EA                       |                   |
| 00078-0659-35               | 2023-Q2 | \$0.00 | EA                       |                   |
| 00078-0659-67               | 2018-Q3 | \$7.72 | EA                       |                   |
| 00078-0659-67               | 2018-Q4 | \$7.72 | EA                       |                   |
| 00078-0659-67               | 2019-Q1 | \$8.48 | EA                       |                   |
| 00078-0659-67               | 2019-Q2 | \$8.48 | EA                       |                   |
| 00078-0659-67               | 2019-Q3 | \$8.48 | EA                       |                   |
| 00078-0659-67               | 2019-Q4 | \$8.48 | EA                       |                   |
| 00078-0659-67               | 2020-Q1 | \$9.07 | EA                       |                   |



**G. Market Data and Revenue and Sales Volume Data**

**Wholesale Acquisition Cost Unit Price**

**Description:** The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Wholesale Acquisition Cost (WAC) unit price of the selected drug.

| National Drug Code (NDC-11) | Quarter | WAC     | Unit type (each, ML, GM) | Total Unit Volume |
|-----------------------------|---------|---------|--------------------------|-------------------|
| 00078-0659-67               | 2020-Q2 | \$9.07  | EA                       |                   |
| 00078-0659-67               | 2020-Q3 | \$9.07  | EA                       |                   |
| 00078-0659-67               | 2020-Q4 | \$9.07  | EA                       |                   |
| 00078-0659-67               | 2021-Q1 | \$9.71  | EA                       |                   |
| 00078-0659-67               | 2021-Q2 | \$9.71  | EA                       |                   |
| 00078-0659-67               | 2021-Q3 | \$9.71  | EA                       |                   |
| 00078-0659-67               | 2021-Q4 | \$9.71  | EA                       |                   |
| 00078-0659-67               | 2022-Q1 | \$10.39 | EA                       |                   |
| 00078-0659-67               | 2022-Q2 | \$10.39 | EA                       |                   |
| 00078-0659-67               | 2022-Q3 | \$10.60 | EA                       |                   |
| 00078-0659-67               | 2022-Q4 | \$10.60 | EA                       |                   |
| 00078-0659-67               | 2023-Q1 | \$11.13 | EA                       |                   |
| 00078-0659-67               | 2023-Q2 | \$11.13 | EA                       |                   |
| 00078-0659-20               | 2018-Q3 | \$7.72  | EA                       |                   |
| 00078-0659-20               | 2018-Q4 | \$7.72  | EA                       |                   |
| 00078-0659-20               | 2019-Q1 | \$8.48  | EA                       |                   |
| 00078-0659-20               | 2019-Q2 | \$8.48  | EA                       |                   |
| 00078-0659-20               | 2019-Q3 | \$8.48  | EA                       |                   |
| 00078-0659-20               | 2019-Q4 | \$8.48  | EA                       |                   |
| 00078-0659-20               | 2020-Q1 | \$9.07  | EA                       |                   |
| 00078-0659-20               | 2020-Q2 | \$9.07  | EA                       |                   |
| 00078-0659-20               | 2020-Q3 | \$9.07  | EA                       |                   |

**G. Market Data and Revenue and Sales Volume Data**

**Wholesale Acquisition Cost Unit Price**

**Description:** The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Wholesale Acquisition Cost (WAC) unit price of the selected drug.

| National Drug Code (NDC-11) | Quarter | WAC     | Unit type (each, ML, GM) | Total Unit Volume |
|-----------------------------|---------|---------|--------------------------|-------------------|
| 00078-0659-20               | 2020-Q4 | \$9.07  | EA                       |                   |
| 00078-0659-20               | 2021-Q1 | \$9.71  | EA                       |                   |
| 00078-0659-20               | 2021-Q2 | \$9.71  | EA                       |                   |
| 00078-0659-20               | 2021-Q3 | \$9.71  | EA                       |                   |
| 00078-0659-20               | 2021-Q4 | \$9.71  | EA                       |                   |
| 00078-0659-20               | 2022-Q1 | \$10.39 | EA                       |                   |
| 00078-0659-20               | 2022-Q2 | \$10.39 | EA                       |                   |
| 00078-0659-20               | 2022-Q3 | \$10.60 | EA                       |                   |
| 00078-0659-20               | 2022-Q4 | \$10.60 | EA                       |                   |
| 00078-0659-20               | 2023-Q1 | \$11.13 | EA                       |                   |
| 00078-0659-20               | 2023-Q2 | \$11.13 | EA                       |                   |
| 00078-0777-61               | 2018-Q3 | \$0.00  | EA                       |                   |
| 00078-0777-61               | 2018-Q4 | \$0.00  | EA                       |                   |
| 00078-0777-61               | 2019-Q1 | \$0.00  | EA                       |                   |
| 00078-0777-61               | 2019-Q2 | \$0.00  | EA                       |                   |
| 00078-0777-61               | 2019-Q3 | \$0.00  | EA                       |                   |
| 00078-0777-61               | 2019-Q4 | \$0.00  | EA                       |                   |
| 00078-0777-61               | 2020-Q1 | \$0.00  | EA                       |                   |
| 00078-0777-61               | 2020-Q2 | \$0.00  | EA                       |                   |
| 00078-0777-61               | 2020-Q3 | \$0.00  | EA                       |                   |
| 00078-0777-61               | 2020-Q4 | \$0.00  | EA                       |                   |
| 00078-0777-61               | 2021-Q1 | \$0.00  | EA                       |                   |

**G. Market Data and Revenue and Sales Volume Data**

**Wholesale Acquisition Cost Unit Price**

**Description:** The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Wholesale Acquisition Cost (WAC) unit price of the selected drug.

| National Drug Code (NDC-11) | Quarter | WAC    | Unit type (each, ML, GM) | Total Unit Volume |
|-----------------------------|---------|--------|--------------------------|-------------------|
| 00078-0777-61               | 2021-Q2 | \$0.00 | EA                       |                   |
| 00078-0777-61               | 2021-Q3 | \$0.00 | EA                       |                   |
| 00078-0777-61               | 2021-Q4 | \$0.00 | EA                       |                   |
| 00078-0777-61               | 2022-Q1 | \$0.00 | EA                       |                   |
| 00078-0777-61               | 2022-Q2 | \$0.00 | EA                       |                   |
| 00078-0777-61               | 2022-Q3 | \$0.00 | EA                       |                   |
| 00078-0777-61               | 2022-Q4 | \$0.00 | EA                       |                   |
| 00078-0777-61               | 2023-Q1 | \$0.00 | EA                       |                   |
| 00078-0777-61               | 2023-Q2 | \$0.00 | EA                       |                   |
| 00078-0777-35               | 2018-Q3 | \$0.00 | EA                       |                   |
| 00078-0777-35               | 2018-Q4 | \$0.00 | EA                       |                   |
| 00078-0777-35               | 2019-Q1 | \$0.00 | EA                       |                   |
| 00078-0777-35               | 2019-Q2 | \$0.00 | EA                       |                   |
| 00078-0777-35               | 2019-Q3 | \$0.00 | EA                       |                   |
| 00078-0777-35               | 2019-Q4 | \$0.00 | EA                       |                   |
| 00078-0777-35               | 2020-Q1 | \$0.00 | EA                       |                   |
| 00078-0777-35               | 2020-Q2 | \$0.00 | EA                       |                   |
| 00078-0777-35               | 2020-Q3 | \$0.00 | EA                       |                   |
| 00078-0777-35               | 2020-Q4 | \$0.00 | EA                       |                   |
| 00078-0777-35               | 2021-Q1 | \$0.00 | EA                       |                   |
| 00078-0777-35               | 2021-Q2 | \$0.00 | EA                       |                   |
| 00078-0777-35               | 2021-Q3 | \$0.00 | EA                       |                   |



**G. Market Data and Revenue and Sales Volume Data**

**Wholesale Acquisition Cost Unit Price**

**Description:** The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Wholesale Acquisition Cost (WAC) unit price of the selected drug.

| National Drug Code (NDC-11) | Quarter | WAC     | Unit type (each, ML, GM) | Total Unit Volume |
|-----------------------------|---------|---------|--------------------------|-------------------|
| 00078-0777-35               | 2021-Q4 | \$0.00  | EA                       |                   |
| 00078-0777-35               | 2022-Q1 | \$0.00  | EA                       |                   |
| 00078-0777-35               | 2022-Q2 | \$0.00  | EA                       |                   |
| 00078-0777-35               | 2022-Q3 | \$0.00  | EA                       |                   |
| 00078-0777-35               | 2022-Q4 | \$0.00  | EA                       |                   |
| 00078-0777-35               | 2023-Q1 | \$0.00  | EA                       |                   |
| 00078-0777-35               | 2023-Q2 | \$0.00  | EA                       |                   |
| 00078-0777-67               | 2018-Q3 | \$7.72  | EA                       |                   |
| 00078-0777-67               | 2018-Q4 | \$7.72  | EA                       |                   |
| 00078-0777-67               | 2019-Q1 | \$8.48  | EA                       |                   |
| 00078-0777-67               | 2019-Q2 | \$8.48  | EA                       |                   |
| 00078-0777-67               | 2019-Q3 | \$8.48  | EA                       |                   |
| 00078-0777-67               | 2019-Q4 | \$8.48  | EA                       |                   |
| 00078-0777-67               | 2020-Q1 | \$9.07  | EA                       |                   |
| 00078-0777-67               | 2020-Q2 | \$9.07  | EA                       |                   |
| 00078-0777-67               | 2020-Q3 | \$9.07  | EA                       |                   |
| 00078-0777-67               | 2020-Q4 | \$9.07  | EA                       |                   |
| 00078-0777-67               | 2021-Q1 | \$9.71  | EA                       |                   |
| 00078-0777-67               | 2021-Q2 | \$9.71  | EA                       |                   |
| 00078-0777-67               | 2021-Q3 | \$9.71  | EA                       |                   |
| 00078-0777-67               | 2021-Q4 | \$9.71  | EA                       |                   |
| 00078-0777-67               | 2022-Q1 | \$10.39 | EA                       |                   |

**G. Market Data and Revenue and Sales Volume Data**

**Wholesale Acquisition Cost Unit Price**

**Description:** The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Wholesale Acquisition Cost (WAC) unit price of the selected drug.

| National Drug Code (NDC-11) | Quarter | WAC     | Unit type (each, ML, GM) | Total Unit Volume |
|-----------------------------|---------|---------|--------------------------|-------------------|
| 00078-0777-67               | 2022-Q2 | \$10.39 | EA                       |                   |
| 00078-0777-67               | 2022-Q3 | \$10.60 | EA                       |                   |
| 00078-0777-67               | 2022-Q4 | \$10.60 | EA                       |                   |
| 00078-0777-67               | 2023-Q1 | \$11.13 | EA                       |                   |
| 00078-0777-67               | 2023-Q2 | \$11.13 | EA                       |                   |
| 00078-0777-20               | 2018-Q3 | \$7.72  | EA                       |                   |
| 00078-0777-20               | 2018-Q4 | \$7.72  | EA                       |                   |
| 00078-0777-20               | 2019-Q1 | \$8.48  | EA                       |                   |
| 00078-0777-20               | 2019-Q2 | \$8.48  | EA                       |                   |
| 00078-0777-20               | 2019-Q3 | \$8.48  | EA                       |                   |
| 00078-0777-20               | 2019-Q4 | \$8.48  | EA                       |                   |
| 00078-0777-20               | 2020-Q1 | \$9.07  | EA                       |                   |
| 00078-0777-20               | 2020-Q2 | \$9.07  | EA                       |                   |
| 00078-0777-20               | 2020-Q3 | \$9.07  | EA                       |                   |
| 00078-0777-20               | 2020-Q4 | \$9.07  | EA                       |                   |
| 00078-0777-20               | 2021-Q1 | \$9.71  | EA                       |                   |
| 00078-0777-20               | 2021-Q2 | \$9.71  | EA                       |                   |
| 00078-0777-20               | 2021-Q3 | \$9.71  | EA                       |                   |
| 00078-0777-20               | 2021-Q4 | \$9.71  | EA                       |                   |
| 00078-0777-20               | 2022-Q1 | \$10.39 | EA                       |                   |
| 00078-0777-20               | 2022-Q2 | \$10.39 | EA                       |                   |
| 00078-0777-20               | 2022-Q3 | \$10.60 | EA                       |                   |

**G. Market Data and Revenue and Sales Volume Data****Wholesale Acquisition Cost Unit Price**

**Description:** The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Wholesale Acquisition Cost (WAC) unit price of the selected drug.

| National Drug Code (NDC-11) | Quarter | WAC     | Unit type (each, ML, GM) | Total Unit Volume |
|-----------------------------|---------|---------|--------------------------|-------------------|
| 00078-0777-20               | 2022-Q4 | \$10.60 | EA                       |                   |
| 00078-0777-20               | 2023-Q1 | \$11.13 | EA                       |                   |
| 00078-0777-20               | 2023-Q2 | \$11.13 | EA                       |                   |
| 00078-0696-61               | 2018-Q3 | \$0.00  | EA                       |                   |
| 00078-0696-61               | 2018-Q4 | \$0.00  | EA                       |                   |
| 00078-0696-61               | 2019-Q1 | \$0.00  | EA                       |                   |
| 00078-0696-61               | 2019-Q2 | \$0.00  | EA                       |                   |
| 00078-0696-61               | 2019-Q3 | \$0.00  | EA                       |                   |
| 00078-0696-61               | 2019-Q4 | \$0.00  | EA                       |                   |
| 00078-0696-61               | 2020-Q1 | \$0.00  | EA                       |                   |
| 00078-0696-61               | 2020-Q2 | \$0.00  | EA                       |                   |
| 00078-0696-61               | 2020-Q3 | \$0.00  | EA                       |                   |
| 00078-0696-61               | 2020-Q4 | \$0.00  | EA                       |                   |
| 00078-0696-61               | 2021-Q1 | \$0.00  | EA                       |                   |
| 00078-0696-61               | 2021-Q2 | \$0.00  | EA                       |                   |
| 00078-0696-61               | 2021-Q3 | \$0.00  | EA                       |                   |
| 00078-0696-61               | 2021-Q4 | \$0.00  | EA                       |                   |
| 00078-0696-61               | 2022-Q1 | \$0.00  | EA                       |                   |
| 00078-0696-61               | 2022-Q2 | \$0.00  | EA                       |                   |
| 00078-0696-61               | 2022-Q3 | \$0.00  | EA                       |                   |
| 00078-0696-61               | 2022-Q4 | \$0.00  | EA                       |                   |
| 00078-0696-61               | 2023-Q1 | \$0.00  | EA                       |                   |



**G. Market Data and Revenue and Sales Volume Data**

**Wholesale Acquisition Cost Unit Price**

**Description:** The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Wholesale Acquisition Cost (WAC) unit price of the selected drug.

| National Drug Code (NDC-11) | Quarter | WAC    | Unit type (each, ML, GM) | Total Unit Volume |
|-----------------------------|---------|--------|--------------------------|-------------------|
| 00078-0696-61               | 2023-Q2 | \$0.00 | EA                       |                   |
| 00078-0696-35               | 2018-Q3 | \$0.00 | EA                       |                   |
| 00078-0696-35               | 2018-Q4 | \$0.00 | EA                       |                   |
| 00078-0696-35               | 2019-Q1 | \$0.00 | EA                       |                   |
| 00078-0696-35               | 2019-Q2 | \$0.00 | EA                       |                   |
| 00078-0696-35               | 2019-Q3 | \$0.00 | EA                       |                   |
| 00078-0696-35               | 2019-Q4 | \$0.00 | EA                       |                   |
| 00078-0696-35               | 2020-Q1 | \$0.00 | EA                       |                   |
| 00078-0696-35               | 2020-Q2 | \$0.00 | EA                       |                   |
| 00078-0696-35               | 2020-Q3 | \$0.00 | EA                       |                   |
| 00078-0696-35               | 2020-Q4 | \$0.00 | EA                       |                   |
| 00078-0696-35               | 2021-Q1 | \$0.00 | EA                       |                   |
| 00078-0696-35               | 2021-Q2 | \$0.00 | EA                       |                   |
| 00078-0696-35               | 2021-Q3 | \$0.00 | EA                       |                   |
| 00078-0696-35               | 2021-Q4 | \$0.00 | EA                       |                   |
| 00078-0696-35               | 2022-Q1 | \$0.00 | EA                       |                   |
| 00078-0696-35               | 2022-Q2 | \$0.00 | EA                       |                   |
| 00078-0696-35               | 2022-Q3 | \$0.00 | EA                       |                   |
| 00078-0696-35               | 2022-Q4 | \$0.00 | EA                       |                   |
| 00078-0696-35               | 2023-Q1 | \$0.00 | EA                       |                   |
| 00078-0696-35               | 2023-Q2 | \$0.00 | EA                       |                   |
| 00078-0696-67               | 2018-Q3 | \$7.72 | EA                       |                   |

**G. Market Data and Revenue and Sales Volume Data**

**Wholesale Acquisition Cost Unit Price**

**Description:** The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Wholesale Acquisition Cost (WAC) unit price of the selected drug.

| National Drug Code (NDC-11) | Quarter | WAC     | Unit type (each, ML, GM) | Total Unit Volume |
|-----------------------------|---------|---------|--------------------------|-------------------|
| 00078-0696-67               | 2018-Q4 | \$7.72  | EA                       |                   |
| 00078-0696-67               | 2019-Q1 | \$8.48  | EA                       |                   |
| 00078-0696-67               | 2019-Q2 | \$8.48  | EA                       |                   |
| 00078-0696-67               | 2019-Q3 | \$8.48  | EA                       |                   |
| 00078-0696-67               | 2019-Q4 | \$8.48  | EA                       |                   |
| 00078-0696-67               | 2020-Q1 | \$9.07  | EA                       |                   |
| 00078-0696-67               | 2020-Q2 | \$9.07  | EA                       |                   |
| 00078-0696-67               | 2020-Q3 | \$9.07  | EA                       |                   |
| 00078-0696-67               | 2020-Q4 | \$9.07  | EA                       |                   |
| 00078-0696-67               | 2021-Q1 | \$9.71  | EA                       |                   |
| 00078-0696-67               | 2021-Q2 | \$9.71  | EA                       |                   |
| 00078-0696-67               | 2021-Q3 | \$9.71  | EA                       |                   |
| 00078-0696-67               | 2021-Q4 | \$9.71  | EA                       |                   |
| 00078-0696-67               | 2022-Q1 | \$10.39 | EA                       |                   |
| 00078-0696-67               | 2022-Q2 | \$10.39 | EA                       |                   |
| 00078-0696-67               | 2022-Q3 | \$10.60 | EA                       |                   |
| 00078-0696-67               | 2022-Q4 | \$10.60 | EA                       |                   |
| 00078-0696-67               | 2023-Q1 | \$11.13 | EA                       |                   |
| 00078-0696-67               | 2023-Q2 | \$11.13 | EA                       |                   |
| 00078-0696-20               | 2018-Q3 | \$7.72  | EA                       |                   |
| 00078-0696-20               | 2018-Q4 | \$7.72  | EA                       |                   |
| 00078-0696-20               | 2019-Q1 | \$8.48  | EA                       |                   |



**G. Market Data and Revenue and Sales Volume Data**

**Wholesale Acquisition Cost Unit Price**

**Description:** The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Wholesale Acquisition Cost (WAC) unit price of the selected drug.

| National Drug Code (NDC-11) | Quarter | WAC     | Unit type (each, ML, GM) | Total Unit Volume |
|-----------------------------|---------|---------|--------------------------|-------------------|
| 00078-0696-20               | 2019-Q2 | \$8.48  | EA                       |                   |
| 00078-0696-20               | 2019-Q3 | \$8.48  | EA                       |                   |
| 00078-0696-20               | 2019-Q4 | \$8.48  | EA                       |                   |
| 00078-0696-20               | 2020-Q1 | \$9.07  | EA                       |                   |
| 00078-0696-20               | 2020-Q2 | \$9.07  | EA                       |                   |
| 00078-0696-20               | 2020-Q3 | \$9.07  | EA                       |                   |
| 00078-0696-20               | 2020-Q4 | \$9.07  | EA                       |                   |
| 00078-0696-20               | 2021-Q1 | \$9.71  | EA                       |                   |
| 00078-0696-20               | 2021-Q2 | \$9.71  | EA                       |                   |
| 00078-0696-20               | 2021-Q3 | \$9.71  | EA                       |                   |
| 00078-0696-20               | 2021-Q4 | \$9.71  | EA                       |                   |
| 00078-0696-20               | 2022-Q1 | \$10.39 | EA                       |                   |
| 00078-0696-20               | 2022-Q2 | \$10.39 | EA                       |                   |
| 00078-0696-20               | 2022-Q3 | \$10.60 | EA                       |                   |
| 00078-0696-20               | 2022-Q4 | \$10.60 | EA                       |                   |
| 00078-0696-20               | 2023-Q1 | \$11.13 | EA                       |                   |
| 00078-0696-20               | 2023-Q2 | \$11.13 | EA                       |                   |

**Explanations:**

- WAC Price is reported as defined in section 1847A(c)(6)(B) of the Act.
- WAC Price and Unit Volume reported at the lowest dispensing unit; Each (tablet).
- WAC Price reported is the WAC Price as of the end of the quarter.

- Total Unit volume is at the lowest selling unit; Each (tablet).
- Total Unit volume excludes free goods, samples, patient assistance programs, and related units.

| G. Market Data and Revenue and Sales Volume Data  |                            |         |                     |           |                   |
|---|----------------------------|---------|---------------------|-----------|-------------------|
| Medicaid Best Price   |                            |         |                     |           |                   |
| <b>Description:</b> The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Medicaid best price of the selected drug. The Medicaid best price information reflects what was submitted to Medicaid under the MDRP in accordance with the Medicaid National Drug Rebate Agreement and as described in section 42 C.F.R. § 447.505 – determination of best price. |                            |         |                     |           |                   |
| Medicaid Best Price   | National Drug Code (NDC-9) | Quarter | Medicaid Best Price | Unit Type | Total Unit Volume |
| Y   | 00078-0659                 | 2018-Q3 |                     | EA        |                   |
| Y   | 00078-0659                 | 2018-Q4 |                     | EA        |                   |
| Y   | 00078-0659                 | 2019-Q1 |                     | EA        |                   |
| Y   | 00078-0659                 | 2019-Q2 |                     | EA        |                   |
| Y   | 00078-0659                 | 2019-Q3 |                     | EA        |                   |
| Y   | 00078-0659                 | 2019-Q4 |                     | EA        |                   |
| Y   | 00078-0659                 | 2020-Q1 |                     | EA        |                   |
| Y   | 00078-0659                 | 2020-Q2 |                     | EA        |                   |
| Y   | 00078-0659                 | 2020-Q3 |                     | EA        |                   |
| Y   | 00078-0659                 | 2020-Q4 |                     | EA        |                   |
| Y   | 00078-0659                 | 2021-Q1 |                     | EA        |                   |
| Y   | 00078-0659                 | 2021-Q2 |                     | EA        |                   |
| Y   | 00078-0659                 | 2021-Q3 |                     | EA        |                   |
| Y   | 00078-0659                 | 2021-Q4 |                     | EA        |                   |
| Y   | 00078-0659                 | 2022-Q1 |                     | EA        |                   |

**G. Market Data and Revenue and Sales Volume Data**

**Medicaid Best Price**

**Description:** The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Medicaid best price of the selected drug. The Medicaid best price information reflects what was submitted to Medicaid under the MDRP in accordance with the Medicaid National Drug Rebate Agreement and as described in section 42 C.F.R. § 447.505 – determination of best price.

| Medicaid Best Price | National Drug Code (NDC-9) | Quarter | Medicaid Best Price | Unit Type | Total Unit Volume |
|---------------------|----------------------------|---------|---------------------|-----------|-------------------|
| Y                   | 00078-0659                 | 2022-Q2 |                     | EA        |                   |
| Y                   | 00078-0659                 | 2022-Q3 |                     | EA        |                   |
| Y                   | 00078-0659                 | 2022-Q4 |                     | EA        |                   |
| Y                   | 00078-0659                 | 2023-Q1 |                     | EA        |                   |
| Y                   | 00078-0659                 | 2023-Q2 |                     | EA        |                   |
| Y                   | 00078-0696                 | 2018-Q3 |                     | EA        |                   |
| Y                   | 00078-0696                 | 2018-Q4 |                     | EA        |                   |
| Y                   | 00078-0696                 | 2019-Q1 |                     | EA        |                   |
| Y                   | 00078-0696                 | 2019-Q2 |                     | EA        |                   |
| Y                   | 00078-0696                 | 2019-Q3 |                     | EA        |                   |
| Y                   | 00078-0696                 | 2019-Q4 |                     | EA        |                   |
| Y                   | 00078-0696                 | 2020-Q1 |                     | EA        |                   |
| Y                   | 00078-0696                 | 2020-Q2 |                     | EA        |                   |
| Y                   | 00078-0696                 | 2020-Q3 |                     | EA        |                   |
| Y                   | 00078-0696                 | 2020-Q4 |                     | EA        |                   |
| Y                   | 00078-0696                 | 2021-Q1 |                     | EA        |                   |
| Y                   | 00078-0696                 | 2021-Q2 |                     | EA        |                   |
| Y                   | 00078-0696                 | 2021-Q3 |                     | EA        |                   |
| Y                   | 00078-0696                 | 2021-Q4 |                     | EA        |                   |
| Y                   | 00078-0696                 | 2022-Q1 |                     | EA        |                   |



**G. Market Data and Revenue and Sales Volume Data**

**Medicaid Best Price**

**Description:** The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Medicaid best price of the selected drug. The Medicaid best price information reflects what was submitted to Medicaid under the MDRP in accordance with the Medicaid National Drug Rebate Agreement and as described in section 42 C.F.R. § 447.505 – determination of best price.

| Medicaid Best Price | National Drug Code (NDC-9) | Quarter | Medicaid Best Price | Unit Type | Total Unit Volume |
|---------------------|----------------------------|---------|---------------------|-----------|-------------------|
| Y                   | 00078-0696                 | 2022-Q2 |                     | EA        |                   |
| Y                   | 00078-0696                 | 2022-Q3 |                     | EA        |                   |
| Y                   | 00078-0696                 | 2022-Q4 |                     | EA        |                   |
| Y                   | 00078-0696                 | 2023-Q1 |                     | EA        |                   |
| Y                   | 00078-0696                 | 2023-Q2 |                     | EA        |                   |
| Y                   | 00078-0777                 | 2018-Q3 |                     | EA        |                   |
| Y                   | 00078-0777                 | 2018-Q4 |                     | EA        |                   |
| Y                   | 00078-0777                 | 2019-Q1 |                     | EA        |                   |
| Y                   | 00078-0777                 | 2019-Q2 |                     | EA        |                   |
| Y                   | 00078-0777                 | 2019-Q3 |                     | EA        |                   |
| Y                   | 00078-0777                 | 2019-Q4 |                     | EA        |                   |
| Y                   | 00078-0777                 | 2020-Q1 |                     | EA        |                   |
| Y                   | 00078-0777                 | 2020-Q2 |                     | EA        |                   |
| Y                   | 00078-0777                 | 2020-Q3 |                     | EA        |                   |
| Y                   | 00078-0777                 | 2020-Q4 |                     | EA        |                   |
| Y                   | 00078-0777                 | 2021-Q1 |                     | EA        |                   |
| Y                   | 00078-0777                 | 2021-Q2 |                     | EA        |                   |
| Y                   | 00078-0777                 | 2021-Q3 |                     | EA        |                   |
| Y                   | 00078-0777                 | 2021-Q4 |                     | EA        |                   |
| Y                   | 00078-0777                 | 2022-Q1 |                     | EA        |                   |

**G. Market Data and Revenue and Sales Volume Data****Medicaid Best Price**

**Description:** The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Medicaid best price of the selected drug. The Medicaid best price information reflects what was submitted to Medicaid under the MDRP in accordance with the Medicaid National Drug Rebate Agreement and as described in section 42 C.F.R. § 447.505 – determination of best price.

| Medicaid Best Price | National Drug Code (NDC-9) | Quarter | Medicaid Best Price | Unit Type | Total Unit Volume |
|---------------------|----------------------------|---------|---------------------|-----------|-------------------|
| Y                   | 00078-0777                 | 2022-Q2 |                     | EA        |                   |
| Y                   | 00078-0777                 | 2022-Q3 |                     | EA        |                   |
| Y                   | 00078-0777                 | 2022-Q4 |                     | EA        |                   |
| Y                   | 00078-0777                 | 2023-Q1 |                     | EA        |                   |
| Y                   | 00078-0777                 | 2023-Q2 |                     | EA        |                   |

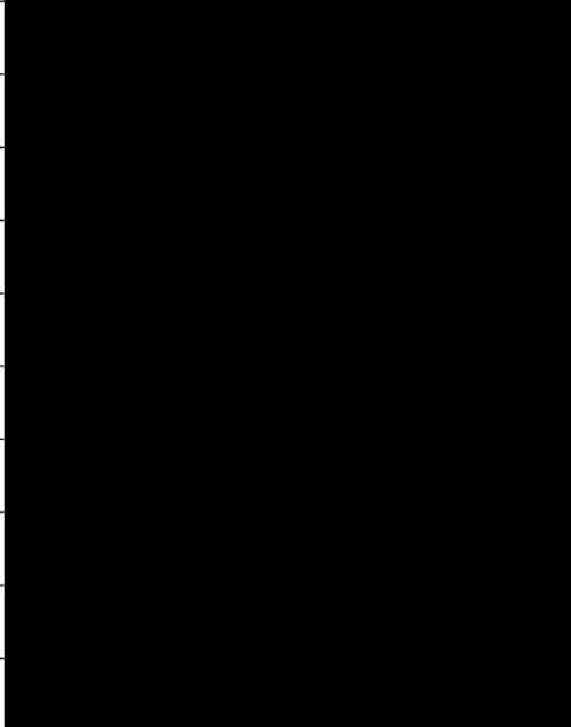
**Explanations:**

- Best Price as defined in 42 U.S.C. § 1396r-8(c) and 42 C.F.R. § 447.505(a) for the corresponding quarter as of 2Q 2023.
- Calculated based on the Company's methodology and Reasonable Assumptions of 42 C.F.R. § 447.505(a).
- Best Price and Unit Volume reported at the lowest dispensing unit; Each (tablet)
- Unit volume is based on the AMP reportable units as submitted to CMS MDP Enterprise portal as of 2Q23

**G. Market Data and Revenue and Sales Volume Data**

**Federal Supply Schedule Price**

**Description:** The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. Manufacturers reported any federal supply schedule (FSS) price for the selected drug made available during the most recent five years. The FSS price information reflects what can be found online in the pharmaceutical pricing data for all VA National Acquisition Center programs.

| Federal Supply Schedule Price | National Drug Code (NDC-11) | Price Start Date to End Date | Federal Supply Schedule Service Price | Unit Type (EA, ML, GM) | Total Unit Volume  |
|-------------------------------|-----------------------------|------------------------------|---------------------------------------|------------------------|--|
| Y                             | 00078-0659-35               | 2018-07-01 - 2018-12-31      | \$6.26                                | EA                     |  |
| Y                             | 00078-0659-35               | 2019-01-01 - 2019-12-31      | \$7.56                                | EA                     |  |
| Y                             | 00078-0777-35               | 2018-07-01 - 2018-12-31      | \$6.26                                | EA                     |  |
| Y                             | 00078-0777-35               | 2019-01-01 - 2019-12-31      | \$7.56                                | EA                     |  |
| Y                             | 00078-0696-35               | 2018-07-01 - 2018-12-31      | \$6.26                                | EA                     |  |
| Y                             | 00078-0696-35               | 2019-01-01 - 2019-12-31      | \$7.56                                | EA                     |  |
| Y                             | 00078-0659-67               | 2018-07-01 - 2018-12-31      | \$6.26                                | EA                     |  |
| Y                             | 00078-0659-67               | 2019-01-01 - 2019-12-31      | \$7.56                                | EA                     |  |
| Y                             | 00078-0659-67               | 2020-01-01 - 2020-08-31      | \$7.69                                | EA                     |  |
| Y                             | 00078-0659-67               | 2020-09-01 - 2020-12-31      | \$8.90                                | EA                     |  |



**G. Market Data and Revenue and Sales Volume Data**

**Federal Supply Schedule Price**

**Description:** The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. Manufacturers reported any federal supply schedule (FSS) price for the selected drug made available during the most recent five years. The FSS price information reflects what can be found online in the pharmaceutical pricing data for all VA National Acquisition Center programs.

| Federal Supply Schedule Price | National Drug Code (NDC-11) | Price Start Date to End Date | Federal Supply Schedule Service Price | Unit Type (EA, ML, GM) | Total Unit Volume |
|-------------------------------|-----------------------------|------------------------------|---------------------------------------|------------------------|-------------------|
| Y                             | 00078-0659-67               | 2021-01-01 - 2021-12-31      | \$8.90                                | EA                     |                   |
| Y                             | 00078-0659-67               | 2022-01-01 - 2022-12-31      | \$9.38                                | EA                     |                   |
| Y                             | 00078-0659-67               | 2023-01-01 - 2023-06-30      | \$10.15                               | EA                     |                   |
| Y                             | 00078-0659-20               | 2018-07-01 - 2018-12-31      | \$6.26                                | EA                     |                   |
| Y                             | 00078-0659-20               | 2019-01-01 - 2019-12-31      | \$7.56                                | EA                     |                   |
| Y                             | 00078-0659-20               | 2020-01-01 - 2020-08-31      | \$7.69                                | EA                     |                   |
| Y                             | 00078-0659-20               | 2020-09-01 - 2020-12-31      | \$8.90                                | EA                     |                   |
| Y                             | 00078-0659-20               | 2021-01-01 - 2021-12-31      | \$8.90                                | EA                     |                   |
| Y                             | 00078-0659-20               | 2022-01-01 - 2022-12-31      | \$9.38                                | EA                     |                   |
| Y                             | 00078-0659-20               | 2023-01-01 - 2023-06-30      | \$10.15                               | EA                     |                   |

**G. Market Data and Revenue and Sales Volume Data**

**Federal Supply Schedule Price**

**Description:** The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. Manufacturers reported any federal supply schedule (FSS) price for the selected drug made available during the most recent five years. The FSS price information reflects what can be found online in the pharmaceutical pricing data for all VA National Acquisition Center programs.

| Federal Supply Schedule Price | National Drug Code (NDC-11) | Price Start Date to End Date | Federal Supply Schedule Service Price | Unit Type (EA, ML, GM) | Total Unit Volume |
|-------------------------------|-----------------------------|------------------------------|---------------------------------------|------------------------|-------------------|
| Y                             | 00078-0777-67               | 2018-07-01 - 2018-12-31      | \$6.26                                | EA                     |                   |
| Y                             | 00078-0777-67               | 2019-01-01 - 2019-12-31      | \$7.56                                | EA                     |                   |
| Y                             | 00078-0777-67               | 2020-01-01 - 2020-08-31      | \$7.69                                | EA                     |                   |
| Y                             | 00078-0777-67               | 2020-09-01 - 2020-12-31      | \$8.90                                | EA                     |                   |
| Y                             | 00078-0777-67               | 2021-01-01 - 2021-12-31      | \$8.90                                | EA                     |                   |
| Y                             | 00078-0777-67               | 2022-01-01 - 2022-12-31      | \$9.38                                | EA                     |                   |
| Y                             | 00078-0777-67               | 2023-01-01 - 2023-06-30      | \$10.15                               | EA                     |                   |
| Y                             | 00078-0777-20               | 2018-07-01 - 2018-12-31      | \$6.26                                | EA                     |                   |
| Y                             | 00078-0777-20               | 2019-01-01 - 2019-12-31      | \$7.56                                | EA                     |                   |
| Y                             | 00078-0777-20               | 2020-01-01 - 2020-08-31      | \$7.69                                | EA                     |                   |



**G. Market Data and Revenue and Sales Volume Data**

**Federal Supply Schedule Price**

**Description:** The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. Manufacturers reported any federal supply schedule (FSS) price for the selected drug made available during the most recent five years. The FSS price information reflects what can be found online in the pharmaceutical pricing data for all VA National Acquisition Center programs.

| Federal Supply Schedule Price | National Drug Code (NDC-11) | Price Start Date to End Date | Federal Supply Schedule Service Price | Unit Type (EA, ML, GM) | Total Unit Volume |
|-------------------------------|-----------------------------|------------------------------|---------------------------------------|------------------------|-------------------|
| Y                             | 00078-0777-20               | 2020-09-01 - 2020-12-31      | \$8.90                                | EA                     |                   |
| Y                             | 00078-0777-20               | 2021-01-01 - 2021-12-31      | \$8.90                                | EA                     |                   |
| Y                             | 00078-0777-20               | 2022-01-01 - 2022-12-31      | \$9.38                                | EA                     |                   |
| Y                             | 00078-0777-20               | 2023-01-01 - 2023-06-30      | \$10.15                               | EA                     |                   |
| Y                             | 00078-0696-67               | 2018-07-01 - 2018-12-31      | \$6.26                                | EA                     |                   |
| Y                             | 00078-0696-67               | 2019-01-01 - 2019-12-31      | \$7.56                                | EA                     |                   |
| Y                             | 00078-0696-67               | 2020-01-01 - 2020-08-31      | \$7.69                                | EA                     |                   |
| Y                             | 00078-0696-67               | 2020-09-01 - 2020-12-31      | \$8.90                                | EA                     |                   |
| Y                             | 00078-0696-67               | 2021-01-01 - 2021-12-31      | \$8.90                                | EA                     |                   |
| Y                             | 00078-0696-67               | 2022-01-01 - 2022-12-31      | \$9.38                                | EA                     |                   |

**G. Market Data and Revenue and Sales Volume Data**

**Federal Supply Schedule Price**

**Description:** The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. Manufacturers reported any federal supply schedule (FSS) price for the selected drug made available during the most recent five years. The FSS price information reflects what can be found online in the pharmaceutical pricing data for all VA National Acquisition Center programs.

| Federal Supply Schedule Price | National Drug Code (NDC-11) | Price Start Date to End Date | Federal Supply Schedule Service Price | Unit Type (EA, ML, GM) | Total Unit Volume |
|-------------------------------|-----------------------------|------------------------------|---------------------------------------|------------------------|-------------------|
| Y                             | 00078-0696-67               | 2023-01-01 - 2023-06-30      | \$10.15                               | EA                     |                   |
| Y                             | 00078-0696-20               | 2018-07-01 - 2018-12-31      | \$6.26                                | EA                     |                   |
| Y                             | 00078-0696-20               | 2019-01-01 - 2019-12-31      | \$7.56                                | EA                     |                   |
| Y                             | 00078-0696-20               | 2020-01-01 - 2020-08-31      | \$7.69                                | EA                     |                   |
| Y                             | 00078-0696-20               | 2020-09-01 - 2020-12-31      | \$8.90                                | EA                     |                   |
| Y                             | 00078-0696-20               | 2021-01-01 - 2021-12-31      | \$8.90                                | EA                     |                   |
| Y                             | 00078-0696-20               | 2022-01-01 - 2022-12-31      | \$9.38                                | EA                     |                   |
| Y                             | 00078-0696-20               | 2023-01-01 - 2023-06-30      | \$10.15                               | EA                     |                   |

**Explanations:**

- Unit Volume is at the lowest dispensing unit; Each (tablet)
- Price is at the at the lowest dispensing unit; Each (tablet)

- Federal Supply Schedule Price is the price charged to Other Government Agencies identified as eligible under the Federal Supply Schedule Agreement 38 U.S.C. § 8126
- Federal Supply Schedule Price is not the price charged to the Big Four (Veterans Administrations, Department of Defense, Coast Guard, and Indian Health) under the Federal Supply Schedule Agreement 38 U.S.C. § 8126
- The Federal Supply Schedule Price is net of the Industrial Funding Fee
- Unit volume is based on units sold to Other Government Agencies as identified as eligible under the Federal Supply Schedule agreement 38 U.S.C. § 8126

| G. Market Data and Revenue and Sales Volume Data   |                             |                              |                |                        |                   |
|--|-----------------------------|------------------------------|----------------|------------------------|-------------------|
| Big Four Price   |                             |                              |                |                        |                   |
| <b>Description:</b> The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Big Four price of the selected drug. The Big Four price information reflects the information that can be found online in the pharmaceutical pricing data for all VA National Acquisition Center programs. |                             |                              |                |                        |                   |
| Big Four Price   | National Drug Code (NDC-11) | Price Start Date to End Date | Big Four Price | Unit Type (EA, ML, GM) | Total Unit Volume |
| Y  | 00078-0659-35               | 2018-07-01 - 2018-12-31      | \$4.72         | EA                     |                   |
| Y  | 00078-0659-35               | 2019-01-01 - 2019-12-31      | \$5.49         | EA                     |                   |
| Y  | 00078-0659-67               | 2018-07-01 - 2018-12-31      | \$4.78         | EA                     |                   |
| Y  | 00078-0659-67               | 2019-01-01 - 2019-12-31      | \$5.27         | EA                     |                   |
| Y  | 00078-0659-67               | 2020-01-01 - 2020-12-31      | \$5.52         | EA                     |                   |
| Y  | 00078-0659-67               | 2021-01-01 - 2021-12-31      | \$6.13         | EA                     |                   |
| Y  | 00078-0659-67               | 2022-01-01 - 2022-12-31      | \$6.91         | EA                     |                   |



**G. Market Data and Revenue and Sales Volume Data****Big Four Price**

**Description:** The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Big Four price of the selected drug. The Big Four price information reflects the information that can be found online in the pharmaceutical pricing data for all VA National Acquisition Center programs.

| Big Four Price | National Drug Code (NDC-11) | Price Start Date to End Date | Big Four Price | Unit Type (EA, ML, GM) | Total Unit Volume |
|----------------|-----------------------------|------------------------------|----------------|------------------------|-------------------|
| Y              | 00078-0659-67               | 2023-01-01 - 2023-06-30      | \$7.58         | EA                     |                   |
| Y              | 00078-0659-20               | 2018-07-01 - 2018-12-31      | \$4.79         | EA                     |                   |
| Y              | 00078-0659-20               | 2019-01-01 - 2019-12-31      | \$5.29         | EA                     |                   |
| Y              | 00078-0659-20               | 2020-01-01 - 2020-12-31      | \$5.51         | EA                     |                   |
| Y              | 00078-0659-20               | 2021-01-01 - 2021-12-31      | \$6.11         | EA                     |                   |
| Y              | 00078-0659-20               | 2022-01-01 - 2022-12-31      | \$6.89         | EA                     |                   |
| Y              | 00078-0659-20               | 2023-01-01 - 2023-06-30      | \$7.57         | EA                     |                   |
| Y              | 00078-0777-35               | 2018-07-01 - 2018-12-31      | \$4.74         | EA                     |                   |
| Y              | 00078-0777-35               | 2019-01-01 - 2019-12-31      | \$5.53         | EA                     |                   |
| Y              | 00078-0777-67               | 2018-07-01 - 2018-12-31      | \$4.80         | EA                     |                   |
| Y              | 00078-0777-67               | 2019-01-01 - 2019-12-31      | \$5.32         | EA                     |                   |

**G. Market Data and Revenue and Sales Volume Data**

**Big Four Price**

**Description:** The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Big Four price of the selected drug. The Big Four price information reflects the information that can be found online in the pharmaceutical pricing data for all VA National Acquisition Center programs.

| Big Four Price | National Drug Code (NDC-11) | Price Start Date to End Date | Big Four Price | Unit Type (EA, ML, GM) | Total Unit Volume |
|----------------|-----------------------------|------------------------------|----------------|------------------------|-------------------|
| Y              | 00078-0777-67               | 2020-01-01 - 2020-12-31      | \$5.50         | EA                     |                   |
| Y              | 00078-0777-67               | 2021-01-01 - 2021-12-31      | \$6.13         | EA                     |                   |
| Y              | 00078-0777-67               | 2022-01-01 - 2022-12-31      | \$6.90         | EA                     |                   |
| Y              | 00078-0777-67               | 2023-01-01 - 2023-06-30      | \$7.62         | EA                     |                   |
| Y              | 00078-0777-20               | 2018-07-01 - 2018-12-31      | \$4.79         | EA                     |                   |
| Y              | 00078-0777-20               | 2019-01-01 - 2019-12-31      | \$5.29         | EA                     |                   |
| Y              | 00078-0777-20               | 2020-01-01 - 2020-12-31      | \$5.51         | EA                     |                   |
| Y              | 00078-0777-20               | 2021-01-01 - 2021-12-31      | \$6.12         | EA                     |                   |
| Y              | 00078-0777-20               | 2022-01-01 - 2022-12-31      | \$6.89         | EA                     |                   |
| Y              | 00078-0777-20               | 2023-01-01 - 2023-06-30      | \$7.56         | EA                     |                   |
| Y              | 00078-0696-35               | 2018-07-01 - 2018-12-31      | \$4.68         | EA                     |                   |

**G. Market Data and Revenue and Sales Volume Data**

**Big Four Price**

**Description:** The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Big Four price of the selected drug. The Big Four price information reflects the information that can be found online in the pharmaceutical pricing data for all VA National Acquisition Center programs.

| Big Four Price | National Drug Code (NDC-11) | Price Start Date to End Date | Big Four Price | Unit Type (EA, ML, GM) | Total Unit Volume |
|----------------|-----------------------------|------------------------------|----------------|------------------------|-------------------|
| Y              | 00078-0696-35               | 2019-01-01 - 2019-12-31      | \$5.57         | EA                     |                   |
| Y              | 00078-0696-67               | 2018-07-01 - 2018-12-31      | \$4.80         | EA                     |                   |
| Y              | 00078-0696-67               | 2019-01-01 - 2019-12-31      | \$5.31         | EA                     |                   |
| Y              | 00078-0696-67               | 2020-01-01 - 2020-12-31      | \$5.51         | EA                     |                   |
| Y              | 00078-0696-67               | 2021-01-01 - 2021-12-31      | \$6.14         | EA                     |                   |
| Y              | 00078-0696-67               | 2022-01-01 - 2022-12-31      | \$6.90         | EA                     |                   |
| Y              | 00078-0696-67               | 2023-01-01 - 2023-06-30      | \$7.61         | EA                     |                   |
| Y              | 00078-0696-20               | 2018-07-01 - 2018-12-31      | \$4.80         | EA                     |                   |
| Y              | 00078-0696-20               | 2019-01-01 - 2019-12-31      | \$5.29         | EA                     |                   |
| Y              | 00078-0696-20               | 2020-01-01 - 2020-12-31      | \$5.51         | EA                     |                   |
| Y              | 00078-0696-20               | 2021-01-01 - 2021-12-31      | \$6.12         | EA                     |                   |



**G. Market Data and Revenue and Sales Volume Data****Big Four Price**

**Description:** The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Big Four price of the selected drug. The Big Four price information reflects the information that can be found online in the pharmaceutical pricing data for all VA National Acquisition Center programs.

| Big Four Price | National Drug Code (NDC-11) | Price Start Date to End Date | Big Four Price | Unit Type (EA, ML, GM) | Total Unit Volume |
|----------------|-----------------------------|------------------------------|----------------|------------------------|-------------------|
| Y              | 00078-0696-20               | 2022-01-01 - 2022-12-31      | \$6.88         | EA                     |                   |
| Y              | 00078-0696-20               | 2023-01-01 - 2023-06-30      | \$7.54         | EA                     |                   |

**Explanations:**

- Unit Volume is at the lowest dispensing unit; Each (tablet)
- Price is at the at the lowest dispensing unit; Each (tablet)
- Big Four price as defined by 38 U.S.C. § 8126
- Big Four Price is the price charged to the Big Four entities (Veterans Administrations, Department of Defense, Coast Guard, and Indian Health) identified eligible under the Federal Supply Schedule Agreement
- Big Four Price is not the price charged to Other Government Agencies identified eligible under the Federal Supply Schedule Agreement
- The Federal Supply Schedule Price is net of the Industrial Funding Fee
- Unit volume is based on units sold to the Big Four price as defined by 38 U.S.C. § 8126

**G. Market Data and Revenue and Sales Volume Data**

**U.S. Commercial Average Net Unit Price**

**Description:** The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides the U.S. commercial average net unit price, including group and individual commercial plans on- and off-exchange of the selected drug.

| National Drug Code (NDC-11) | Quarter | U.S. Commercial Average Unit Net Price | U.S. Commercial Average Net Unit Price - Without Patient Assistance Programs | U.S. Commercial Average Net Unit Price- Best | Unit type (EA, ML, GM) | Total Unit Volume |
|-----------------------------|---------|--|--|--|------------------------|-------------------|
| 00078-0659-20               | 2018-Q3 |  |  |  | EA                     |                   |
| 00078-0659-20               | 2018-Q4 |  |  |  | EA                     |                   |
| 00078-0659-20               | 2019-Q1 |  |  |  | EA                     |                   |
| 00078-0659-20               | 2019-Q2 |  |  |  | EA                     |                   |
| 00078-0659-20               | 2019-Q3 |  |  |  | EA                     |                   |
| 00078-0659-20               | 2019-Q4 |  |  |  | EA                     |                   |
| 00078-0659-20               | 2020-Q1 |  |  |  | EA                     |                   |
| 00078-0659-20               | 2020-Q2 |  |  |  | EA                     |                   |
| 00078-0659-20               | 2020-Q3 |  |  |  | EA                     |                   |
| 00078-0659-20               | 2020-Q4 |  |  |  | EA                     |                   |
| 00078-0659-20               | 2021-Q1 |  |  |  | EA                     |                   |
| 00078-0659-20               | 2021-Q2 |  |  |  | EA                     |                   |
| 00078-0659-20               | 2021-Q3 |  |  |  | EA                     |                   |
| 00078-0659-20               | 2021-Q4 |  |  |  | EA                     |                   |
| 00078-0659-20               | 2022-Q1 |  |  |  | EA                     |                   |
| 00078-0659-20               | 2022-Q2 |  |  |  | EA                     |                   |
| 00078-0659-20               | 2022-Q3 |  |  |  | EA                     |                   |
| 00078-0659-20               | 2022-Q4 |  |  |  | EA                     |                   |
| 00078-0659-20               | 2023-Q1 |  |  |  | EA                     |                   |
| 00078-0659-20               | 2023-Q2 |  |  |  | EA                     |                   |



**G. Market Data and Revenue and Sales Volume Data**

**U.S. Commercial Average Net Unit Price**

**Description:** The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides the U.S. commercial average net unit price, including group and individual commercial plans on- and off-exchange of the selected drug.

| National Drug Code (NDC-11) | Quarter | U.S. Commercial Average Unit Net Price | U.S. Commercial Average Net Unit Price - Without Patient Assistance Programs | U.S. Commercial Average Net Unit Price- Best | Unit type (EA, ML, GM) | Total Unit Volume |
|-----------------------------|---------|--|--|--|------------------------|-------------------|
| 00078-0659-35               | 2018-Q3 |  |  |  | EA                     |                   |
| 00078-0659-35               | 2018-Q4 |  |  |  | EA                     |                   |
| 00078-0659-35               | 2019-Q1 |  |  |  | EA                     |                   |
| 00078-0659-35               | 2019-Q2 |  |  |  | EA                     |                   |
| 00078-0659-35               | 2019-Q3 |  |  |  | EA                     |                   |
| 00078-0659-35               | 2019-Q4 |  |  |  | EA                     |                   |
| 00078-0659-35               | 2020-Q1 |  |  |  | EA                     |                   |
| 00078-0659-35               | 2020-Q2 |  |  |  | EA                     |                   |
| 00078-0659-35               | 2020-Q3 |  |  |  | EA                     |                   |
| 00078-0659-35               | 2020-Q4 |  |  |  | EA                     |                   |
| 00078-0659-35               | 2021-Q1 |  |  |  | EA                     |                   |
| 00078-0659-35               | 2021-Q2 |  |  |  | EA                     |                   |
| 00078-0659-35               | 2021-Q3 |  |  |  | EA                     |                   |
| 00078-0659-35               | 2021-Q4 |  |  |  | EA                     |                   |
| 00078-0659-35               | 2022-Q1 |  |  |  | EA                     |                   |
| 00078-0659-35               | 2022-Q2 |  |  |  | EA                     |                   |
| 00078-0659-35               | 2022-Q3 |  |  |  | EA                     |                   |
| 00078-0659-35               | 2022-Q4 |  |  |  | EA                     |                   |
| 00078-0659-35               | 2023-Q1 |  |  |  | EA                     |                   |
| 00078-0659-35               | 2023-Q2 |  |  |  | EA                     |                   |

**G. Market Data and Revenue and Sales Volume Data**

**U.S. Commercial Average Net Unit Price**

**Description:** The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides the U.S. commercial average net unit price, including group and individual commercial plans on- and off-exchange of the selected drug.

| National Drug Code (NDC-11) | Quarter | U.S. Commercial Average Unit Net Price | U.S. Commercial Average Net Unit Price - Without Patient Assistance Programs | U.S. Commercial Average Net Unit Price- Best | Unit type (EA, ML, GM) | Total Unit Volume |
|-----------------------------|---------|--|--|--|------------------------|-------------------|
| 00078-0659-67               | 2018-Q3 |  |  |  | EA                     |                   |
| 00078-0659-67               | 2018-Q4 |  |  |  | EA                     |                   |
| 00078-0659-67               | 2019-Q1 |  |  |  | EA                     |                   |
| 00078-0659-67               | 2019-Q2 |  |  |  | EA                     |                   |
| 00078-0659-67               | 2019-Q3 |  |  |  | EA                     |                   |
| 00078-0659-67               | 2019-Q4 |  |  |  | EA                     |                   |
| 00078-0659-67               | 2020-Q1 |  |  |  | EA                     |                   |
| 00078-0659-67               | 2020-Q2 |  |  |  | EA                     |                   |
| 00078-0659-67               | 2020-Q3 |  |  |  | EA                     |                   |
| 00078-0659-67               | 2020-Q4 |  |  |  | EA                     |                   |
| 00078-0659-67               | 2021-Q1 |  |  |  | EA                     |                   |
| 00078-0659-67               | 2021-Q2 |  |  |  | EA                     |                   |
| 00078-0659-67               | 2021-Q3 |  |  |  | EA                     |                   |
| 00078-0659-67               | 2021-Q4 |  |  |  | EA                     |                   |
| 00078-0659-67               | 2022-Q1 |  |  |  | EA                     |                   |
| 00078-0659-67               | 2022-Q2 |  |  |  | EA                     |                   |
| 00078-0659-67               | 2022-Q3 |  |  |  | EA                     |                   |
| 00078-0659-67               | 2022-Q4 |  |  |  | EA                     |                   |
| 00078-0659-67               | 2023-Q1 |  |  |  | EA                     |                   |
| 00078-0659-67               | 2023-Q2 |  |  |  | EA                     |                   |

**G. Market Data and Revenue and Sales Volume Data**

**U.S. Commercial Average Net Unit Price**

**Description:** The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides the U.S. commercial average net unit price, including group and individual commercial plans on- and off-exchange of the selected drug.

| National Drug Code (NDC-11) | Quarter | U.S. Commercial Average Unit Net Price | U.S. Commercial Average Net Unit Price - Without Patient Assistance Programs | U.S. Commercial Average Net Unit Price- Best | Unit type (EA, ML, GM) | Total Unit Volume |
|-----------------------------|---------|--|--|--|------------------------|-------------------|
| 00078-0696-20               | 2018-Q3 |  |  |  | EA                     |                   |
| 00078-0696-20               | 2018-Q4 |  |  |  | EA                     |                   |
| 00078-0696-20               | 2019-Q1 |  |  |  | EA                     |                   |
| 00078-0696-20               | 2019-Q2 |  |  |  | EA                     |                   |
| 00078-0696-20               | 2019-Q3 |  |  |  | EA                     |                   |
| 00078-0696-20               | 2019-Q4 |  |  |  | EA                     |                   |
| 00078-0696-20               | 2020-Q1 |  |  |  | EA                     |                   |
| 00078-0696-20               | 2020-Q2 |  |  |  | EA                     |                   |
| 00078-0696-20               | 2020-Q3 |  |  |  | EA                     |                   |
| 00078-0696-20               | 2020-Q4 |  |  |  | EA                     |                   |
| 00078-0696-20               | 2021-Q1 |  |  |  | EA                     |                   |
| 00078-0696-20               | 2021-Q2 |  |  |  | EA                     |                   |
| 00078-0696-20               | 2021-Q3 |  |  |  | EA                     |                   |
| 00078-0696-20               | 2021-Q4 |  |  |  | EA                     |                   |
| 00078-0696-20               | 2022-Q1 |  |  |  | EA                     |                   |
| 00078-0696-20               | 2022-Q2 |  |  |  | EA                     |                   |
| 00078-0696-20               | 2022-Q3 |  |  |  | EA                     |                   |
| 00078-0696-20               | 2022-Q4 |  |  |  | EA                     |                   |
| 00078-0696-20               | 2023-Q1 |  |  |  | EA                     |                   |
| 00078-0696-20               | 2023-Q2 |  |  |  | EA                     |                   |



**G. Market Data and Revenue and Sales Volume Data**

**U.S. Commercial Average Net Unit Price**

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|-----------------------------|---------|--|--|--|------------------------|-------------------|
| 00078-0696-35               | 2018-Q3 |  |  |  | EA                     |                   |
| 00078-0696-35               | 2018-Q4 |  |  |  | EA                     |                   |
| 00078-0696-35               | 2019-Q1 |  |  |  | EA                     |                   |
| 00078-0696-35               | 2019-Q2 |  |  |  | EA                     |                   |
| 00078-0696-35               | 2019-Q3 |  |  |  | EA                     |                   |
| 00078-0696-35               | 2019-Q4 |  |  |  | EA                     |                   |
| 00078-0696-35               | 2020-Q1 |  |  |  | EA                     |                   |
| 00078-0696-35               | 2020-Q2 |  |  |  | EA                     |                   |
| 00078-0696-35               | 2020-Q3 |  |  |  | EA                     |                   |
| 00078-0696-35               | 2020-Q4 |  |  |  | EA                     |                   |
| 00078-0696-35               | 2021-Q1 |  |  |  | EA                     |                   |
| 00078-0696-35               | 2021-Q2 |  |  |  | EA                     |                   |
| 00078-0696-35               | 2021-Q3 |  |  |  | EA                     |                   |
| 00078-0696-35               | 2021-Q4 |  |  |  | EA                     |                   |
| 00078-0696-35               | 2022-Q1 |  |  |  | EA                     |                   |
| 00078-0696-35               | 2022-Q2 |  |  |  | EA                     |                   |
| 00078-0696-35               | 2022-Q3 |  |  |  | EA                     |                   |
| 00078-0696-35               | 2022-Q4 |  |  |  | EA                     |                   |
| 00078-0696-35               | 2023-Q1 |  |  |  | EA                     |                   |
| 00078-0696-35               | 2023-Q2 |  |  |  | EA                     |                   |

**G. Market Data and Revenue and Sales Volume Data**

**U.S. Commercial Average Net Unit Price**

**Description:** The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides the U.S. commercial average net unit price, including group and individual commercial plans on- and off-exchange of the selected drug.

| National Drug Code (NDC-11) | Quarter | U.S. Commercial Average Unit Net Price | U.S. Commercial Average Net Unit Price - Without Patient Assistance Programs | U.S. Commercial Average Net Unit Price- Best | Unit type (EA, ML, GM) | Total Unit Volume |
|-----------------------------|---------|--|--|--|------------------------|-------------------|
| 00078-0696-67               | 2018-Q3 |  |  |  | EA                     |                   |
| 00078-0696-67               | 2018-Q4 |  |  |  | EA                     |                   |
| 00078-0696-67               | 2019-Q1 |  |  |  | EA                     |                   |
| 00078-0696-67               | 2019-Q2 |  |  |  | EA                     |                   |
| 00078-0696-67               | 2019-Q3 |  |  |  | EA                     |                   |
| 00078-0696-67               | 2019-Q4 |  |  |  | EA                     |                   |
| 00078-0696-67               | 2020-Q1 |  |  |  | EA                     |                   |
| 00078-0696-67               | 2020-Q2 |  |  |  | EA                     |                   |
| 00078-0696-67               | 2020-Q3 |  |  |  | EA                     |                   |
| 00078-0696-67               | 2020-Q4 |  |  |  | EA                     |                   |
| 00078-0696-67               | 2021-Q1 |  |  |  | EA                     |                   |
| 00078-0696-67               | 2021-Q2 |  |  |  | EA                     |                   |
| 00078-0696-67               | 2021-Q3 |  |  |  | EA                     |                   |
| 00078-0696-67               | 2021-Q4 |  |  |  | EA                     |                   |
| 00078-0696-67               | 2022-Q1 |  |  |  | EA                     |                   |
| 00078-0696-67               | 2022-Q2 |  |  |  | EA                     |                   |
| 00078-0696-67               | 2022-Q3 |  |  |  | EA                     |                   |
| 00078-0696-67               | 2022-Q4 |  |  |  | EA                     |                   |
| 00078-0696-67               | 2023-Q1 |  |  |  | EA                     |                   |
| 00078-0696-67               | 2023-Q2 |  |  |  | EA                     |                   |



**G. Market Data and Revenue and Sales Volume Data**

**U.S. Commercial Average Net Unit Price**

**Description:** The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides the U.S. commercial average net unit price, including group and individual commercial plans on- and off-exchange of the selected drug.

| National Drug Code (NDC-11) | Quarter | U.S. Commercial Average Unit Net Price | U.S. Commercial Average Net Unit Price - Without Patient Assistance Programs | U.S. Commercial Average Net Unit Price- Best | Unit type (EA, ML, GM) | Total Unit Volume |
|-----------------------------|---------|--|--|--|------------------------|-------------------|
| 00078-0777-20               | 2018-Q3 |  |  |  | EA                     |                   |
| 00078-0777-20               | 2018-Q4 |  |  |  | EA                     |                   |
| 00078-0777-20               | 2019-Q1 |  |  |  | EA                     |                   |
| 00078-0777-20               | 2019-Q2 |  |  |  | EA                     |                   |
| 00078-0777-20               | 2019-Q3 |  |  |  | EA                     |                   |
| 00078-0777-20               | 2019-Q4 |  |  |  | EA                     |                   |
| 00078-0777-20               | 2020-Q1 |  |  |  | EA                     |                   |
| 00078-0777-20               | 2020-Q2 |  |  |  | EA                     |                   |
| 00078-0777-20               | 2020-Q3 |  |  |  | EA                     |                   |
| 00078-0777-20               | 2020-Q4 |  |  |  | EA                     |                   |
| 00078-0777-20               | 2021-Q1 |  |  |  | EA                     |                   |
| 00078-0777-20               | 2021-Q2 |  |  |  | EA                     |                   |
| 00078-0777-20               | 2021-Q3 |  |  |  | EA                     |                   |
| 00078-0777-20               | 2021-Q4 |  |  |  | EA                     |                   |
| 00078-0777-20               | 2022-Q1 |  |  |  | EA                     |                   |
| 00078-0777-20               | 2022-Q2 |  |  |  | EA                     |                   |
| 00078-0777-20               | 2022-Q3 |  |  |  | EA                     |                   |
| 00078-0777-20               | 2022-Q4 |  |  |  | EA                     |                   |
| 00078-0777-20               | 2023-Q1 |  |  |  | EA                     |                   |
| 00078-0777-20               | 2023-Q2 |  |  |  | EA                     |                   |

**G. Market Data and Revenue and Sales Volume Data**

**U.S. Commercial Average Net Unit Price**

**Description:** The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides the U.S. commercial average net unit price, including group and individual commercial plans on- and off-exchange of the selected drug.

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|-----------------------------|---------|--|--|--|------------------------|-------------------|
| 00078-0777-35               | 2018-Q3 |  |  |  | EA                     |                   |
| 00078-0777-35               | 2018-Q4 |  |  |  | EA                     |                   |
| 00078-0777-35               | 2019-Q1 |  |  |  | EA                     |                   |
| 00078-0777-35               | 2019-Q2 |  |  |  | EA                     |                   |
| 00078-0777-35               | 2019-Q3 |  |  |  | EA                     |                   |
| 00078-0777-35               | 2019-Q4 |  |  |  | EA                     |                   |
| 00078-0777-35               | 2020-Q1 |  |  |  | EA                     |                   |
| 00078-0777-35               | 2020-Q2 |  |  |  | EA                     |                   |
| 00078-0777-35               | 2020-Q3 |  |  |  | EA                     |                   |
| 00078-0777-35               | 2020-Q4 |  |  |  | EA                     |                   |
| 00078-0777-35               | 2021-Q1 |  |  |  | EA                     |                   |
| 00078-0777-35               | 2021-Q2 |  |  |  | EA                     |                   |
| 00078-0777-35               | 2021-Q3 |  |  |  | EA                     |                   |
| 00078-0777-35               | 2021-Q4 |  |  |  | EA                     |                   |
| 00078-0777-35               | 2022-Q1 |  |  |  | EA                     |                   |
| 00078-0777-35               | 2022-Q2 |  |  |  | EA                     |                   |
| 00078-0777-35               | 2022-Q3 |  |  |  | EA                     |                   |
| 00078-0777-35               | 2022-Q4 |  |  |  | EA                     |                   |
| 00078-0777-35               | 2023-Q1 |  |  |  | EA                     |                   |
| 00078-0777-35               | 2023-Q2 |  |  |  | EA                     |                   |

**G. Market Data and Revenue and Sales Volume Data**

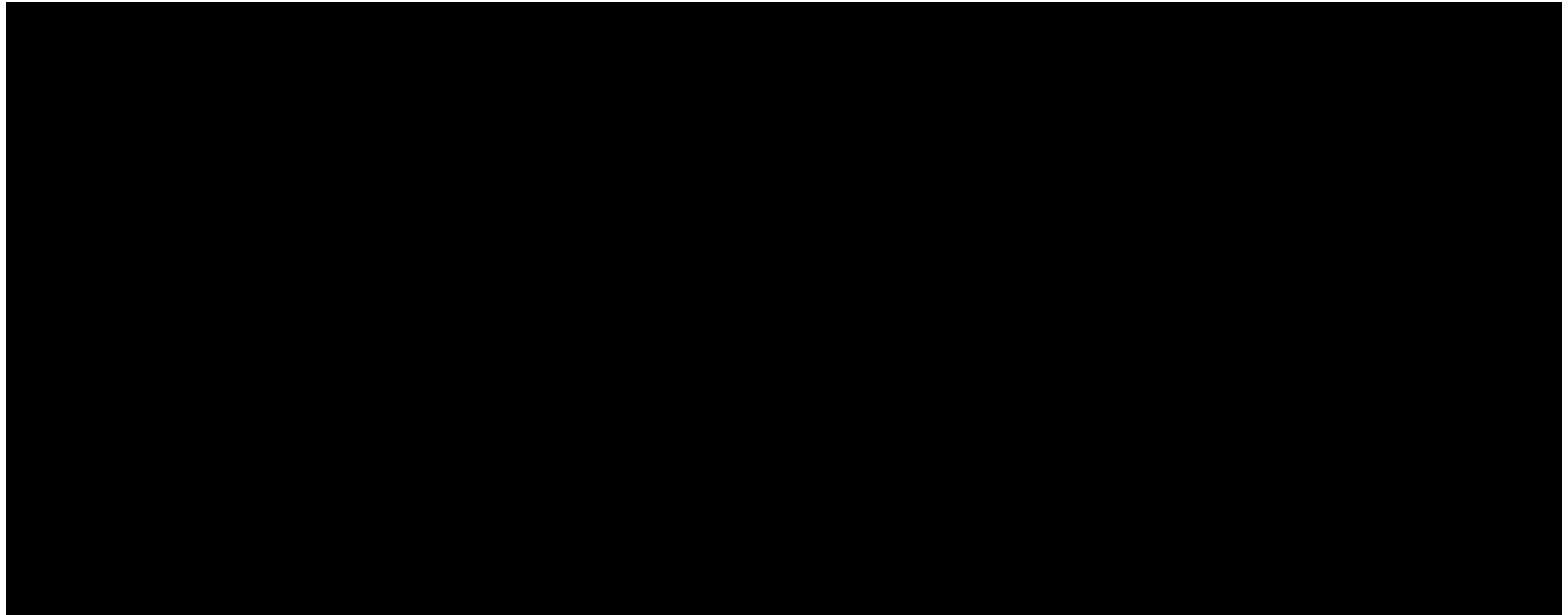
**U.S. Commercial Average Net Unit Price**

**Description:** The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides the U.S. commercial average net unit price, including group and individual commercial plans on- and off-exchange of the selected drug.

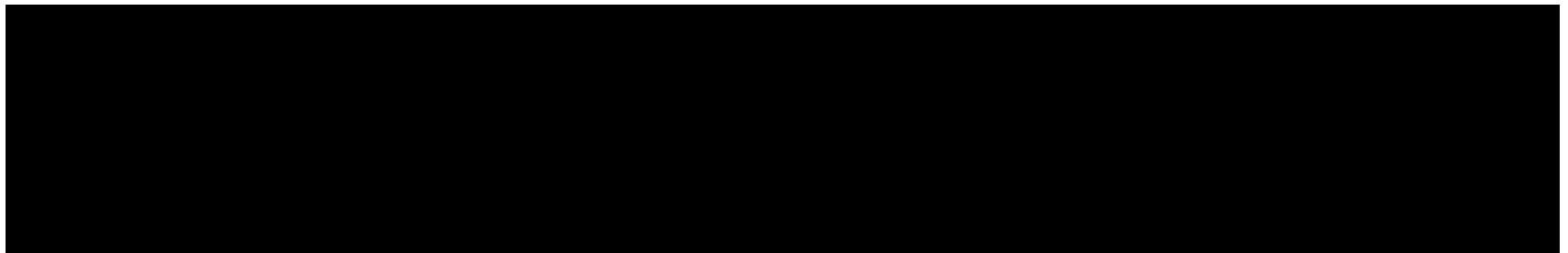
| National Drug Code (NDC-11) | Quarter | U.S. Commercial Average Unit Net Price | U.S. Commercial Average Net Unit Price - Without Patient Assistance Programs | U.S. Commercial Average Net Unit Price- Best | Unit type (EA, ML, GM) | Total Unit Volume |
|-----------------------------|---------|--|--|--|------------------------|-------------------|
| 00078-0777-67               | 2018-Q3 |  |  |  | EA                     |                   |
| 00078-0777-67               | 2018-Q4 |  |  |  | EA                     |                   |
| 00078-0777-67               | 2019-Q1 |  |  |  | EA                     |                   |
| 00078-0777-67               | 2019-Q2 |  |  |  | EA                     |                   |
| 00078-0777-67               | 2019-Q3 |  |  |  | EA                     |                   |
| 00078-0777-67               | 2019-Q4 |  |  |  | EA                     |                   |
| 00078-0777-67               | 2020-Q1 |  |  |  | EA                     |                   |
| 00078-0777-67               | 2020-Q2 |  |  |  | EA                     |                   |
| 00078-0777-67               | 2020-Q3 |  |  |  | EA                     |                   |
| 00078-0777-67               | 2020-Q4 |  |  |  | EA                     |                   |
| 00078-0777-67               | 2021-Q1 |  |  |  | EA                     |                   |
| 00078-0777-67               | 2021-Q2 |  |  |  | EA                     |                   |
| 00078-0777-67               | 2021-Q3 |  |  |  | EA                     |                   |
| 00078-0777-67               | 2021-Q4 |  |  |  | EA                     |                   |
| 00078-0777-67               | 2022-Q1 |  |  |  | EA                     |                   |
| 00078-0777-67               | 2022-Q2 |  |  |  | EA                     |                   |
| 00078-0777-67               | 2022-Q3 |  |  |  | EA                     |                   |
| 00078-0777-67               | 2022-Q4 |  |  |  | EA                     |                   |
| 00078-0777-67               | 2023-Q1 |  |  |  | EA                     |                   |
| 00078-0777-67               | 2023-Q2 |  |  |  | EA                     |                   |

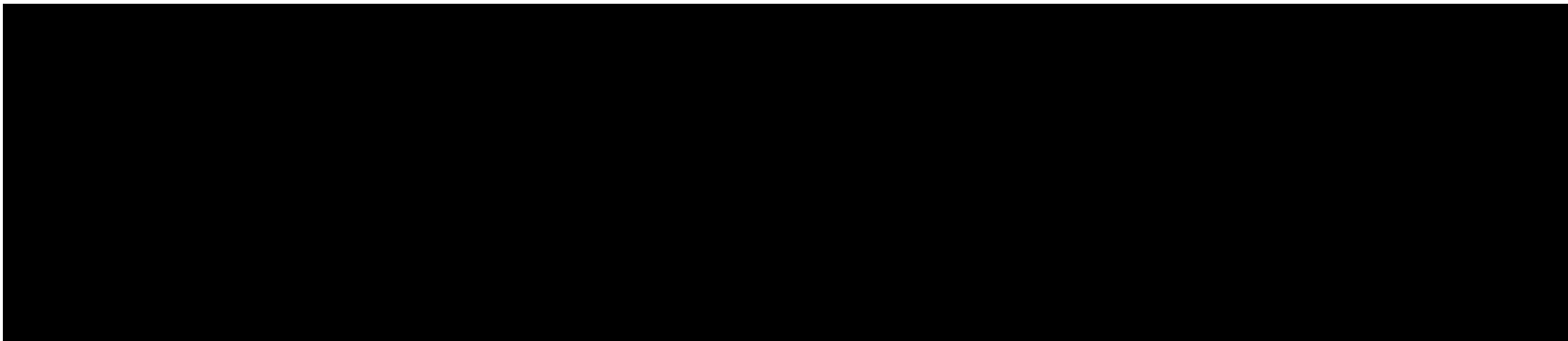
**Explanations:**

U.S. Commercial Average Unit Net Price

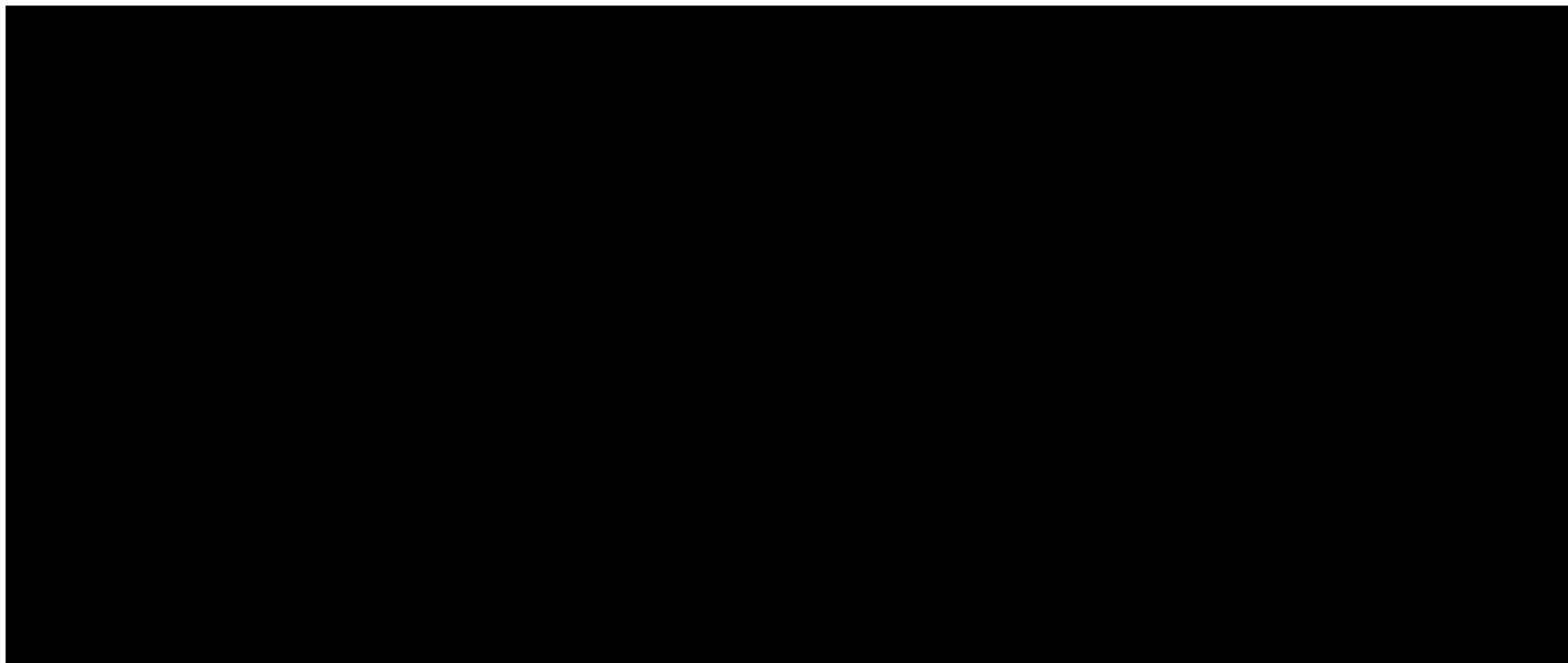


U.S. Commercial Average Net Unit Price - Without Patient Assistance Programs





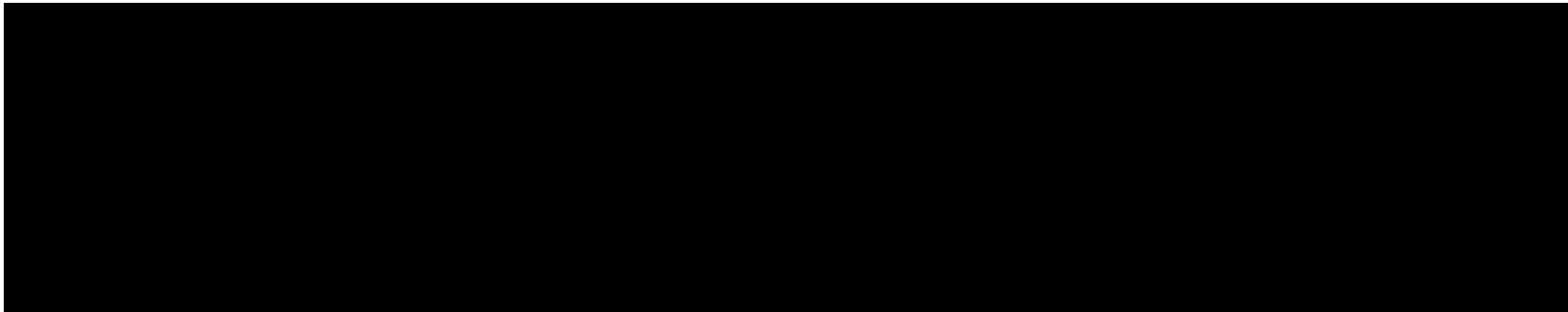
U.S. Commercial Average Net Unit Price - Best







Total Unit Volume



Manufacturer E2 Submissions – Novartis



| Question                                   | Sub-Question                      | Response   |
|--|-----------------------------------|--|
| Question 26:<br>Respondent<br>Information  | Selected Drug                     | VALSARTAN / SACUBITRILAT   |
|  | Respondent Name                   | Suriyanarayanan Janarthanan  |
|  | Organization Name (if applicable) | Novartis   |
|  | Respondent Email                  | suriyanarayanan.janarthanan@novartis.com   |
|  | Who is completing this form?      |  |
| Question 27:<br>Prescribing<br>Information | Prescribing Information           | <p>Entresto® (sacubitril/valsartan) is indicated to reduce the risk of cardiovascular (CV) death and hospitalization for heart failure (HF) in adults with chronic HF (CHF); benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal (Novartis Pharmaceuticals Corporation 1). Additionally, Entresto is approved for treatment of symptomatic HF with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older (Novartis Pharmaceuticals Corporation 1).</p> <p>Entresto is available in three different strengths (24/26mg, 49/51mg, and 97/103mg tablets) and should be taken twice per day (Novartis Pharmaceuticals Corporation 1). A 30-day equivalent supply of Entresto contains 60 tablets. All Entresto tablets are priced at the same wholesale acquisition cost (WAC), regardless of strength.</p> <p>HF is a progressive disease characterized by the heart's inability to pump enough blood to meet the needs of the body. Insufficient blood flow to vital organs (e.g., lungs) leads to worsening symptoms and increased risk of life-threatening complications and death. The fraction of blood that your heart pumps with each beat is called an ejection fraction (EF), and an LVEF of approximately 60% or higher is considered normal (Lang et al. 7) . HF is divided into subtypes based on a patient's LVEF. HF with reduced ejection fraction (HFrEF) is categorized as an LVEF <math>\leq 40\%</math>, HF with mildly reduced ejection fraction (HFmrEF) as an LVEF 41%-49%, and HF with preserved ejection fraction (HFpEF) as an LVEF <math>\geq 50\%</math>. Despite these definitions, LVEF is a variable measure and the FDA approved label recommends using clinical judgement when deciding whom to treat with Entresto (Novartis Pharmaceuticals Corporation 1). HFrEF represents the overwhelming majority of Entresto utilization (~90% of Entresto prescription volume, based on internal estimates). As a result, the evidence presented here will primarily focus on the use of Entresto for the treatment of HFrEF.</p> <p>KEY SUMMARY:</p> <p>1. Entresto's dual mechanism of action through a synergistic combination of two drug components (angiotensin receptor-neprilysin inhibitor, ARNi) make it more than a legacy renin-angiotensin system inhibitor (RASi), and uniquely</p> |

| Question | Sub-Question | Response   |
|----------|--------------|--|
|          |              | <p>effective in helping patients stay out of the hospital and live longer (Dargad et al. 2).</p> <p>2. The 2022 American Heart Association / American College of Cardiology / Heart Failure Society of America (AHA/ACC/HFSA) Guideline for the Management of HF elevated Entresto to a Class IA recommendation for use before legacy RASi classes, angiotensin converting enzyme inhibitor (ACEi) and angiotensin receptor blocker (ARB), and recommends patients switch from ACEi or ARB to Entresto for superior clinical benefits in patients with HFrEF (Heidenreich et al. e309).</p> <p>3. The guideline recommends use of four distinct drug classes (“quadruple therapy”) for the treatment of patients with HFrEF. These four drugs are meant to be used together and are complementary, non-overlapping, non-interchangeable, and additive in their clinical benefits.</p> <p>THERE ARE NO THERAPEUTIC ALTERNATIVE(S) FOR ENTRESTO:</p> <p>Entresto is the first and only ARNi approved by the Food and Drug Administration (FDA) for the treatment of CHF patients with LVEF below normal, with no currently available therapeutic alternative. Entresto is part of the RASi category of medications, which include an ACEi or an ARB. However, Entresto is more than a legacy RASi because it contains two active moieties that target complementary pathways (valsartan, which targets the renin-angiotensin system [RAS] and sacubitril, which targets the natriuretic peptide [NPs] pathway). The older ACEi and ARB classes help control blood pressure and the amount of fluid in the body, but Entresto, by targeting both the RAS and NP pathways, relaxes blood vessels, improves blood flow, and reduces the stress and overactivation of the heart (i.e., Entresto boosts the body’s innate systems to put itself back into balance) (Dargad et al. 2). A component of Entresto, sacubitril, is not available on the market as a standalone medication and is the only neprilysin inhibitor available for HF patients. Entresto is designed specifically to offset the dysregulated pathophysiology of HF for CHF patients (McMurray et al. 2; Pina et al. 46).</p> <p>The 2022 AHA/ACC/HFSA HF Treatment Guideline recommends use of quadruple therapy (four medication classes working together) for treatment of patients with HFrEF (Heidenreich et al. e309). These four medication classes include: Entresto (ARNi), sodium-glucose cotransporter-2 inhibitors (SGLT2i), mineralocorticoid receptor antagonists (MRAs), and evidence-based beta-blockers (BB) (Heidenreich et al. e309). All four drug classes are complementary, non-overlapping in their mechanisms of action, non-interchangeable for one another, and additive in their clinical benefits for patients with HFrEF. These four drug classes have received the highest class of recommendation, Class IA, by the Guideline and are meant to be used together, much in the same way that chemotherapy combinations are meant to be used together for the treatment of certain cancers.</p> <p>The former RASi standards of care, ACEi and ARB, were FDA approved based on placebo-controlled clinical trials in the 1990s. As evidenced by the landmark head-to-head clinical trials, PARADIGM-HF, PIONEER-HF, and PARAGON-HF,</p> |



| Question | Sub-Question | Response   |
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|          |              | <p>Entresto is the only drug that has demonstrated superiority by direct comparison with ACEis/ARBs, in reducing CV death and HF hospitalizations in adult CHF patients with LVEF below normal (Heidenreich et al. e303; McMurray et al. 9; Velazquez et al. 7; Solomon et al. 5),. Due to the overwhelming benefits of Entresto over enalapril (an ACEi), PARADIGM-HF was stopped early. While PARADIGM-HF and PIONEER-HF met their primary endpoints for superiority versus active-comparator, PARAGON-HF narrowly missed the primary endpoint. However, within the prespecified subgroup of patients with a LVEF <math>\leq 57\%</math>, Entresto demonstrated superior risk reduction for HF hospitalization (McMurray et al. 10).</p> <p>Following PARADIGM-HF, an open question remained if Entresto could be safely and effectively started in HFrEF patients hospitalized with acute decompensated HF. High levels of N-terminal pro b-type natriuretic peptide (NT-proBNP) in the bloodstream are typically found in HF patients. PIONEER-HF, a United States (US)-based clinical trial in patients hospitalized with acute HFrEF (36% of participants self-identified as Black), demonstrated a superior reduction in NT-proBNP and in a post-hoc analysis showed a 44% risk reduction for re-hospitalizations in Entresto-treated patients compared to enalapril (an ACEi). Safety was comparable between the two groups (Velazquez et al. 8).</p> <p>Entresto was then studied in HF patients with an LVEF <math>\geq 45\%</math> in PARAGON-HF and demonstrated a greater reduction in HF hospitalizations for patients with an LVEF <math>\leq 57\%</math> compared to valsartan (an ARB). Women, who made up more than half of the participants enrolled in PARAGON-HF, had a lower rate of hospitalization up to a higher LVEF than men when treated with Entresto compared to ARBs (Solomon et al. 3).</p> <p>TAKE-AWAY: Entresto has replaced legacy RASi (ACEi/ARBs) as the new standard of care for the treatment of adult CHF patients with a LVEF less than normal. There are no therapeutic alternatives for Entresto given its unique dual mechanism of action, overwhelming data showing clinical superiority to the former standard of care, and position as a preferred guideline recommended treatment for patients with HFrEF.</p> <p>ENTRESTO HAS REPLACED ACEI AND ARBS AS THE FIRST CHOICE RASI FOR THE TREATMENT OF ADULTS WITH CHF:</p> <p>Prior to Entresto's FDA approval in 2015, ACEi/ARBs were the only RASi treatment options for HF (Yancy, Jessup, Bozkurt, Butler, Casey, Drazner, et al. 28-30). In 2013, the American College of Cardiology Foundation (ACCF) and AHA guidelines recommended that patients with HFrEF receive treatment with either ACEi or ARB, as well as an MRA and an evidence-based BB (Yancy, Jessup, Bozkurt, Butler, Casey, Drazner, et al. 28-32). Following approval of Entresto in 2015, the 2016 ACC/AHA/HFSA Focused Update on New Pharmacologic Therapy for Heart Failure stated that the introduction of an ARNi "represents a milestone in the evolution of care for patients with HF" (Yancy, Jessup, et al. "2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American</p> |

| Question | Sub-Question | Response   |
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|          |              | <p>Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America" 4). This update recommended that HFrEF patients who tolerate an ACEi, or ARB be switched to an ARNi (Entresto) to further reduce morbidity and mortality (Yancy, Jessup, et al. "2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America" 4-5). This recommendation was re-affirmed in the 2017 Focused Guideline Update (Yancy, Jessup, et al. "2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America" 8-9).</p> <p>The 2022 ACC/AHA/HFSA Treatment Guideline for the Management of HF represented the first comprehensive update since 2013 and serves as the most current HF Guideline endorsed by the three major CV medical societies in the US. Notably, the 2022 Guideline elevated Entresto to a Class IA first-choice medication and reaffirmed the recommendation to switch HFrEF patients currently on ACEi or ARB to Entresto based on superior evidence that Entresto further reduces CV death and hospitalization for HF (Heidenreich et al. e302). Furthermore, Entresto should also be initiated de novo in patients hospitalized with acute HFrEF before discharge in the absence of contraindications (Heidenreich et al. e303). Analyses have shown that optimal implementation of Entresto instead of ACEi/ARBs can prevent an estimated 28,484 deaths a year (Fonarow et al. 1).</p> <p>With the expanded label of Entresto in February 2021, the 2022 Treatment Guidelines provided a recommendation for patients with HFpEF, stating that "ARNi may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum" (Heidenreich et al. e328).</p> <p>TAKE-AWAY: The three major CV societies in the US have established and recommend Entresto as an essential, first-choice medication for HFrEF.</p> <p>SGLT2i, MRAs, BBS ARE NOT REPLACEMENTS FOR ARNI:</p> <p>The 2022 HF Treatment Guideline recommends use of quadruple therapy (four medication classes working together) for treatment of patients with HFrEF because of the complementary mechanism of action and benefits of these medications (Heidenreich et al. e266). In addition, the Guideline does not provide recommendations comparing ARNi with SGLT2i, MRAs, or BBs, nor does it advise any sequencing of one drug class before, or instead of, the other (Heidenreich et al. e305-e07). The FDA approvals of SGLT2i, MRA, and BB were established based on placebo-controlled clinical trials. None of these medication classes were evaluated in a head-to-head setting for the treatment of HFrEF. The only direct comparison of medication classes tested were ARNi (Entresto) versus ACEi for the treatment</p> |



| Question | Sub-Question | Response   |
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|          |              | <p>of patients with HFrEF (Solomon et al. 5; Velazquez et al. 8; McMurray et al. 9).</p> <p>TAKE-AWAY: Entresto is an essential and irreplaceable medication for the treatment of CHF patients with a Class IA recommendation as part of quadruple combination therapy for HFrEF patients.</p> <p>Dargad, R. R., et al. "Sacubitril/valsartan: A novel angiotensin receptor-neprilysin inhibitor." Indian Heart J 70 Suppl 1.Suppl 1 (2018): S102-S10. Print.</p> <p>Fonarow, G. C., et al. "Potential Mortality Reduction With Optimal Implementation of Angiotensin Receptor Neprilysin Inhibitor Therapy in Heart Failure." JAMA Cardiol 1.6 (2016): 714-7. Print.</p> <p>Heidenreich, P. A., et al. "2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines." J Am Coll Cardiol 79.17 (2022): e263-e421. Print.</p> <p>Lang, R. M., et al. "Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging." J Am Soc Echocardiogr 28.1 (2015): 1-39 e14. Print.</p> <p>McMurray, J. J., et al. "Angiotensin-neprilysin inhibition versus enalapril in heart failure." N Engl J Med 371.11 (2014): 993-1004. Print.</p> <p>Novartis Pharmaceuticals Corporation. "ENTRESTO." 2021. Print.</p> <p>Pina, I. L., et al. "Improvement of Health Status Following Initiation of Sacubitril/Valsartan in Heart Failure and Reduced Ejection Fraction." JACC Heart Fail 9.1 (2021): 42-51. Print.</p> <p>Solomon, S. D., et al. "Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction." N Engl J Med 381.17 (2019): 1609-20. Print.</p> <p>Velazquez, E. J., et al. "Angiotensin-Neprilysin Inhibition in Acute Decompensated Heart Failure." N Engl J Med 380.6 (2019): 539-48. Print.</p> <p>Yancy, C. W., et al. "2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America." Circulation 134.13 (2016): e282-93. Print.</p> <p>Yancy, C. W., et al. "2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America." Circulation 136.6 (2017): e137-e61. Print.</p> <p>Yancy, C. W., et al. "2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines." Circulation 128.16 (2013): e240-327. Print.</p> |

| Question   | Sub-Question   | Response   |
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|  | Evidence Submitted include a cost-effectiveness measure? | N  |
|  | What type of Evidence is shown?                          |  |
| Question 28:<br>Therapeutic Impact and Comparative Effectiveness | Therapeutic Impact and Comparative Effectiveness         | <p>As explained in our response to Question 27, Entresto has no therapeutic alternative and has replaced angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARBs) as the new standard-of-care renin-angiotensin system inhibitor (RASi) for treatment of adult chronic heart failure (CHF) in the United States (US) for patients with left ventricular ejection fraction (LVEF) below normal. Entresto's dual mechanism of action through a synergistic combination of two drug components (angiotensin receptor-neprilysin inhibitor, ARNi) make it more than a legacy RASi and uniquely effective in helping patients stay out of the hospital and live a longer, higher quality life.</p> <p>KEY SUMMARY:</p> <ol style="list-style-type: none"> <li>1. The therapeutic impact of Entresto in reducing cardiovascular (CV) mortality and HF hospitalizations in adults with CHF and LVEF below normal is clearly demonstrated in both pivotal clinical trials and real-world evidence.</li> <li>2. Entresto has a comparable safety and tolerability profile while providing superior clinical efficacy versus treatment with the former standards of care, ACEi and ARB.</li> <li>3. Entresto significantly improves outcomes that are important to CHF patients, including symptom reduction, improved physical and social functioning, and higher quality of life.</li> <li>4. Entresto is a high-value therapy that has delivered medical cost savings for the US healthcare system.</li> </ol> <p>ENTRESTO HAS DEMONSTRATED CLINICAL SUPERIORITY OVER ACEI/ARBS IN REDUCING DEATH AND HF HOSPITALIZATIONS FOR ADULTS WITH CHF IN PATIENTS WITH LVEF BELOW NORMAL IN BOTH CLINICAL TRIALS AND REAL-WORLD SETTINGS:</p> <p>In PARADIGM-HF, a Phase 3 pivotal trial that formed the basis of the initial US Food and Drug Administration (FDA) approval of Entresto in 2015, Entresto demonstrated a 20% risk reduction in the primary endpoint of CV mortality and hospitalization for HF vs. enalapril (an ACEi) (hazard ratio [HR]: 0.80, 95% CI: 0.73-0.87, p&lt;0.001) in adult patients with HF and reduced ejection fraction (HFrEF) [1]. Entresto was also found to be more effective than enalapril in reducing all-cause mortality by 16% (HR:0.84, 95% CI: 0.76-0.93, p&lt;0.001) [1]. The PARADIGM-HF trial was stopped early after a median of 27 months follow-up because the pre-specified boundary for an overwhelming benefit with Entresto had been crossed [1]. The magnitude of the therapeutic benefit with Entresto seen in PARADIGM-HF was highly significant and clinically important because it was proven superior to the former standard of care, enalapril, in reducing CV death and HF hospitalizations.</p> |



| Question | Sub-Question | Response   |
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|          |              | <ul style="list-style-type: none"> <li>• In 2021, the US FDA granted a label expansion to Entresto to include adult HF patients with preserved ejection fraction (HFpEF) and mildly reduced ejection fraction (HFmrEF) who have a LVEF below normal. The expanded label approval was based on the totality of evidence from PARAGON-HF, a Phase 3 pivotal trial in HFpEF patients, and a pre-specified pooled analysis of PARADIGM-HF and PARAGON-HF. In PARAGON-HF, Entresto reduced the rate of the primary composite endpoint of total HF hospitalization and CV death by 13% relative to the active comparator valsartan (an ARB), but narrowly missed statistical significance (risk ratio [RR]: 0.87; 95% CI: 0.75-1.101) [2]. Prespecified subgroup analyses found a greater treatment benefit of Entresto in patients with LVEF below 57% (RR:0.79; 95% CI: 0.64-0.95) [2].</li> <li>• The prespecified pooled analysis of PARADIGM-HF and PARAGON-HF demonstrated a clinically meaningful benefit of Entresto over enalapril/valsartan across the spectrum of LVEF up to normal levels. Compared to the enalapril/valsartan reference group, a 16% risk reduction for the composite primary outcome of first HF hospitalization or CV death was observed with Entresto treatment [HR: 0.84, 95% CI: 0.78-0.90] in the combined cohort [3]. Entresto was also found superior to enalapril/valsartan in reducing the risks for CV death (HR 0.84; 95% CI, 0.76-0.92), HF hospitalization (HFH) (HR 0.84; 95% CI, 0.77-0.91), all-cause mortality (HR 0.88; 95% CI, 0.81-0.96), total HFH and CV death (RR 0.82; 95% CI, 0.75-0.89), and total HFH (RR 0.81; 95% CI, 0.73-0.90) (Figure 1) [3]. Results that are to the left of the 1.0 ratio line indicate the significant benefit of Entresto compared to enalapril/valsartan.</li> <li>• In addition, Figure 2 shows that taking Entresto compared to enalapril (an ACEi), or valsartan (an ARB), reduced the risk of total HF hospitalizations and CV death in women (gray line) up to a higher LVEF than men (black line). The gray line remained below the threshold of RR=1 to a higher LVEF than the black line indicating the benefit of Entresto compared to enalapril or valsartan [3].</li> </ul> <p>If Entresto were studied against a placebo, the magnitude of the benefit could have been much larger. A putative placebo modeling analysis estimated that a 43% risk reduction (HR:0.57, 95% CI: 0.50-0.66, p&lt;0.0001) in CV death and HF hospitalization could be expected from treatment with Entresto in HFrEF patients if it had been compared to placebo [4]. An updated putative placebo modeling analysis reinforced the treatment benefits of Entresto in reducing HF hospitalizations and mortality across the full range of LVEF. Entresto provided a 38% risk reduction in first HF hospitalization or CV death (RR:0.72; 95% CI: 0.54-0.82, p&lt;0.001) relative to putative placebo across the spectrum of LVEF [5].</p> <p>Robust data on real-world effectiveness of Entresto has been generated since its FDA approval, demonstrating that the clinical advantages of Entresto over ACEi/ARBs seen in phase 3 pivotal trials are generalizable to diverse CHF populations in routine clinical practice in the US. Several of these high-quality studies are summarized below.</p> |

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|          |              | <ul style="list-style-type: none"> <li>• In a large retrospective cohort study of systolic (left ventricular) HF patients treated with Entresto or ACEi/ARBs from July 2015 through February 2018, patients treated with Entresto had significantly lower risks of all-cause mortality (HR:0.80, 95% CI: 0.66-0.97, p=0.027) and all-cause hospitalization (HR: 0.86; 95% CI: 0.80-0.91, p&lt;0.001) [6].</li> <li>• In a cohort of veterans diagnosed with HFrEF, those who switched from ACEi/ARBs to Entresto had significantly fewer all-cause hospitalizations than those who continued with ACEi/ARBs at 4-month follow-up [adjusted risk ratio: 0.80; 95% CI: 0.65, 0.98, p=0.035] [7].</li> <li>• In a retrospective study of real-world patients with HF and LVEF below normal (≤60%) receiving care at a multi-state healthcare system, Entresto use was associated with lower risks for all-cause hospitalizations (odds ratio [OR]:0.51; 95% CI: 0.43-0.60), HF hospitalizations (OR: 0.57, 95% CI: 0.43-0.76), and HF-related Emergency Department (ED) visits (OR: 0.53; 95% CI: 0.42-0.67) compared to ACEi/ARBs use (Figure 3) [8] [Novartis data on File].</li> </ul> <p>TAKE-AWAY: The significant therapeutic impact of Entresto in reducing mortality and HF hospitalizations established Entresto as the new standard-of-care RASi for treatment of adult CHF with LVEF below normal. Evidence demonstrates that the use of Entresto® can lead to a 12% lower risk of all-cause mortality and 19% lowered risk of HF-hospitalizations, compared to the use of ACEi/ARBs in patients with HF [3].</p> <p>ENTRESTO SIGNIFICANTLY IMPROVES PATIENT-REPORTED OUTCOMES AMONG PATIENTS WITH HFrEF IN AS EARLY AS 2 MONTHS, WITH BENEFITS PERSISTING THROUGH 18 MONTHS:</p> <p>In both clinical trials and high-quality prospective observational studies, Entresto treated HFrEF patients experienced significant improvements in self-reported symptoms, physical function, social function, and quality of life [9-12].</p> <p>The 12-question Kansas City Cardiomyopathy Questionnaire (KCCQ-12) is a well-validated HF-specific patient-reported outcome (PRO) instrument that measures patients' health status. It consists of four domains:</p> <ul style="list-style-type: none"> <li>• Physical limitation (KCCQ-PL);</li> <li>• Social limitation (KCCQ-SL);</li> <li>• Symptom frequency (KCCQ-SF); and</li> <li>• Quality of life (KCCQ-QoL).</li> </ul> <p>A KCCQ overall summary (KCCQ-OS) score can be derived as the average of the four domain scores. At the patient-level, a 5-point increase is considered a clinically meaningful improvement and a 10- and 15-point increase represent large and very large improvements, respectively [13].</p> |



| Question | Sub-Question | Response   |
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|          |              | <p>An early analysis from CHAMP-HF Registry, a multicenter, observational registry that captures the care and outcomes of ~5,000 outpatients with HFrEF in the US [9], found that, overall, Entresto patients experienced an average of a 5.3 point (SD: 18.6) improvement in the KCCQ-OS compared with 2.5 points (SD:17.4) for their no-ARNi counterparts [adj. mean diff: 2.9; 95% CI: (1.1-4.6), p=0.001] over a median of 57 days. The proportions of the Entresto group versus the no Entresto group with ≥10-point (large) and ≥20-point (very large) improvements in KCCQ-OS were 32.7% versus 26.9%, respectively, and 20.5% versus 12.1%, respectively [9].</p> <p>In addition, greater improvements were observed across the individual domains in the Entresto group than the no Entresto group: KCCQ-PL [mean (SD): 4.8 (24.8) vs. 2.0 (22.2)], KCCQ-SL [5.9 (26.0) vs. 3.6 (23.8)], KCCQ-SF [4.3 (20.8) vs. 1.5 (21.2)], and KCCQ-QoL [6.4 (23.9) vs. 2.7 (24.1)] [9]. An updated CHAMP-HF analysis with 18-month follow-up later confirmed that the early benefits of Entresto (in as early as 2 months) in improving PROs seen in the previous analysis persisted through 18 months [10].</p> <p>Consistent with the two CHAMP-HF analyses, evidence from several other high-quality studies also support the use of Entresto for improving PROs in HFrEF patients [1; 14; 12].,</p> <p>TAKE-AWAY: Entresto not only helps patients live longer and stay out of the hospital, it also significantly improves their quality of life.</p> <p>ENTRESTO HAS DEMONSTRATED A CONSISTENT TOLERABILITY AND SAFETY PROFILE COMPARABLE TO THAT OF ACEI AND ARBS:</p> <p>Over a nine-year period of randomized clinical trials, beginning with PARADIGM-HF in 2014 through PARAGLIDE-HF in 2023, Entresto has shown similar rates of hyperkalemia, cough, dizziness, and renal failure as compared to ACEi and ARBs [1; 2; 15; 16]. Somewhat greater hypotension tends to occur with Entresto treatment compared to ACEi and ARBs, given that Entresto contains two active components that individually and synergistically contribute to greater blood pressure lowering effects. This is an advantageous effect for HF patients with the common comorbidity of hypertension. Hypotension can usually be addressed by adjusting the dose of diuretic or other antihypertensive medications, managing fluid status, or adjusting the Entresto dose.</p> <p>TAKE-AWAY: Entresto has proven to be a well-tolerated medication with a comparable safety profile and superior clinical efficacy to the former standard of care ACEi/ARBs.</p> <p>ENTRESTO IS A HIGH-VALUE THERAPY WITH A PROVEN TRACK RECORD OF REDUCING HOSPITALIZATIONS AND</p> |



| Question | Sub-Question | Response   |
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|          |              | <p>OFFSETTING MEDICAL COSTS FOR TREATMENT OF HFREF:</p> <p>Entresto is widely recognized as a high-value therapy that has been proven to reduce hospitalizations and associated medical costs for treatment of HFrEF. When assessing the value of a medication, the total cost of care (medical + pharmacy costs) must be considered.</p> <p>The 2022 HF Treatment Guideline states that “in patients with chronic symptomatic HFrEF, treatment with an ARNI instead of an ACEi provides high economic value” [17]. This “high economic value” designation was based on high-quality modeling studies, which extrapolated the efficacy data from PARADIGM-HF and PIONEER-HF into expected cost savings from avoided (re)hospitalizations if eligible HFrEF patients were to receive Entresto instead of enalapril [18; 19]. Specifically:</p> <ul style="list-style-type: none"> <li>• Gaziano et al estimated that for every 1,000 stable outpatients with HFrEF (i.e., PARADIGM-HF alike population) receiving Entresto instead of enalapril, the 21% risk reduction for HF hospitalizations would translate into \$1.3 million savings in 1 year, which would offset nearly 30% of the increased medication cost associated with Entresto (based on Entresto wholesale acquisition cost [WAC] in 2015) [20].</li> <li>• For hospitalized patients with HFrEF (i.e., PIONEER-HF alike population), starting Entresto in the hospital vs. continuing enalapril was projected to save the healthcare system \$452 per person per year because the cost savings from reducing HF rehospitalizations by 44% would far exceed the additional medication costs associated with Entresto (based on Entresto WAC in 2019) [21]. Adopting Entresto in hospitalized HFrEF patients could avert &gt;50,000 HF hospitalizations in the US, saving \$92.3 million annually [21].</li> </ul> <p>In addition to modeling studies, real-world effects of Entresto in reducing hospitalizations and lowering medical costs in HFrEF have been well documented:</p> <ul style="list-style-type: none"> <li>• MEDICARE FEE FOR SERVICE (FFS) POPULATION: A real-world evidence study found that optimizing utilization of Entresto for beneficiaries with HFrEF could lower total Medicare Part A &amp; B expenditures and improve provider performance under the Medicare Shared Savings Program (MSSP) and Bundled Payment for Care Improvement (BPCI) [22]. Among beneficiaries cared for by an MSSP participant, those treated with Entresto had lower annual total Part A &amp; B expenditures than propensity score matched control patients on ACEi/ARBs [mean diff. (95% CI): -\$875 (-\$1,650, -\$101)] and those who received no RASi [mean diff. (95% CI): -\$9,369 (-\$11,376, -\$7,361)] in the framework of MSSP [22]. In the BPCI analysis, the 90-day CHF episode costs for patients treated with Entresto were \$447 (95% CI: -\$1,227 - \$333) less than those who received ACEi/ARBs and \$10,249 (95% CI: -\$11,376, -\$7,361) less than those receiving no RASi [22].</li> </ul> |

| Question                               | Sub-Question  | Response  |
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|  |   | <ul style="list-style-type: none"> <li>• COMMERCIAL AND MEDICARE ADVANTAGE POPULATIONS: An early real-world evidence study of HFrEF patients treated with Entresto or ACEi/ARBs between October 2015 and June 2016 showed that treatment with Entresto resulted in lower all-cause medical costs per patient per month (\$2,273 vs \$3,980; <math>p &lt; 0.05</math>) and total cost-of-care per patient per month (\$3,220 vs. \$4,495, <math>p &lt; 0.05</math>) compared to those treated with ACEi/ARBs [23].</li> <li>• COMMERCIALLY INSURED POPULATION: In a value-based contracting agreement with Prime Therapeutics, a 22% reduction or \$10,117 savings in total cost of care was observed over a 12-month period among patients with HFrEF newly initiating and adherent to Entresto [24]. Hospitalization costs, ED costs, and office visit costs were all significantly reduced after Entresto use versus the pre-index period (69%, 30.1% and 13.3%, respectively, all <math>p</math> values <math>&lt; 0.01</math>) [24]. This study also found significantly reduced hospitalizations and ED visits in the post-index period (63.3% and 43.9%, respectively, <math>p &lt; 0.01</math>) [24].</li> </ul> <p>TAKE-AWAY: In determining a value-based price for Entresto, CMS must look beyond drug cost and consider the economic benefit that Entresto provides in offsetting medical costs.</p> |
|  | Hyperlink to Citation - Additional Materials for Question 28            |   |
|  | Hyperlink to Table/Charts/Graphs - Additional Materials for Question 28 |   |
|  | Evidence Submitted include a cost-effectiveness measure?                | N   |
|  | What type of Evidence is shown?   |   |
| Question 29: Comparative Effectiveness | Response to Question 29   | <p>ENTRESTO HAS SAVED THE LIVES OF MEDICARE BENEFICIARIES SINCE THE FDA FIRST APPROVED ITS USE IN ADULT HFREF</p> <p>Entresto has been found to improve overall survival of Medicare patients living with heart failure with reduced</p>  |



| Question                | Sub-Question | Response  |
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| on Specific Populations |              | <p>ejection fraction (HFrEF) in several real-world evidence studies, when compared to treatment with the former RASi standard of care, angiotensin-converting enzyme inhibitors (ACEi)/angiotensin II receptor blockers (ARBs).</p> <ul style="list-style-type: none"> <li>• <b>MEDICARE FEE-FOR-SERVICE (FFS) BENEFICIARIES:</b> In a large cohort of elderly Medicare FFS beneficiaries (mean age= ~76 years) with HFrEF, inclusive of over 30% women, Entresto-treated patients had a 27% lower risk of death compared to their counterparts treated with ACEi and ARB (95% CI: 0.67-0.80) [1].</li> <li>• <b>MEDICARE PATIENTS HOSPITALIZED FOR HFREF:</b> Greene et al were the first to evaluate clinical effectiveness of Entresto among Medicare FFS patients hospitalized for HFrEF [2]. Using Get With The Guideline (GWTG)-HF Registry (a heart failure [HF] hospital quality improvement program established by American Heart Association [AHA]) data linked with Medicare claims, Greene et al found that older Medicare patients prescribed Entresto upon hospital discharge had a lower post-discharge mortality rate at 1-year compared to patients prescribed ACEi/ARB at discharge (hazard ratio [HR]:0.82; 95% CI: 0.72-0.94) [2]. A more recent study using the same linked GWTG-HF Medicare dataset showed that Medicare patients prescribed Entresto as a first line option upon hospital discharge were able to spend an average of 27 more days at home (95% CI: 12.4 - 41.6 days) and had lower overall mortality rate at 1 year than patients discharged home without Entresto (HR: 0.74, 95% CI: 0.61 – 0.91) [3]. Notably, AHA has added “ARNi at hospital discharge” as an HF Quality Measure to the GWTG-HF program [4].</li> <li>• <b>MEDICARE ADVANTAGE ENROLLEES:</b> In a claims study of privately insured and Medicare Advantage enrollees in a large national United States (US) health plan, a 20% risk reduction in overall mortality was seen for Entresto-treated vs. ACEi/ARB-treated HFrEF patients [5].</li> </ul> <p>TAKE-AWAY: Compelling real-world evidence supports a “direct-to-Entresto” approach for treatment of HFrEF in older Medicare patients.</p> <p>ENTRESTO ADDRESSES THE ONGOING HEALTH DISPARITIES IN HF OUTCOMES BY GENDER, RACE AND ETHNICITY:</p> <p>Health disparities in HF are well-documented. For example, among patients with HF, black patients have higher rates of HF hospitalization compared with white patients and other groups [6-8]. Several studies support current recommendations for the use of Entresto for HFrEF, regardless of race and ethnicity. PIONEER-HF, a US-based clinical trial, included 36% of subjects who self-identified as Black [9]. The results of a subgroup analysis by race reflected consistently beneficial effect of Entresto, as compared with enalapril (an ACEi), in terms of reductions in N-terminal pro b-type natriuretic peptide (NT-proBNP), the primary efficacy outcome [9]. In an analysis of CHAMP-HF, a large registry of outpatients with HFrEF, the association between ARNi initiation and outcomes did not differ by race and ethnicity, supporting the use of Entresto in HFrEF patients irrespective of race and ethnicity [6]. Furthermore, in a pre-</p> |



| Question | Sub-Question | Response   |
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|          |              | <p>specified subgroup analysis of PARAGON-HF, there was a suggestion of treatment heterogeneity with possible benefit of Entresto in women with HFpEF across the left ventricular ejection fraction (LVEF) spectrum [6].</p> <p>TAKE-AWAY: Health disparities may be minimized by increased use of guideline-directed medical therapy, including use of Entresto for patients with HFrEF.</p> <p>OPTIMIZING UTILIZATION OF ENTRESTO FOR ELIGIBLE MEDICARE BENEFICIARIES IS DIRECTLY ALIGNED WITH CMS'S MISSION TO IMPROVE QUALITY OF CARE AT A LOWER COST:</p> <p>The study conducted by Albert et al was the first peer-reviewed study that utilized health insurance claims data to assess the impact of Entresto utilization on total cost of care. The study compared rates of hospitalization and cost of care between 279 HFrEF patients treated with Entresto, and their matched controls treated with ACEi/ARB. The majority (75%) of the patients included were enrolled in a Medicare Advantage plan. The study found that patients treated with Entresto had significantly lower all-cause medical costs per patient per month (PPPM) compared to those treated with ACEi/ARB (mean PPPM costs: \$2,273 vs. \$3,980). These medical cost savings more than offset the additional pharmacy costs from Entresto use, resulting in a net savings of \$1,275 PPPM in total cost of care for Entresto treated patients compared to ACEi/ARB treated patients [10].</p> <p>A more recent study conducted after the label expansion of Entresto in 2021 showed that Entresto lowered all-cause medical costs by \$4,959 over a 12-month period in a cohort of 7,658 Medicare Advantage patients with chronic heart failure when compared to the 12-month period before Entresto initiation. The medical cost savings were also consistently observed across various subgroups, including patients with concomitant use of mineralocorticoid receptor antagonists (MRA) or sodium-glucose cotransporter-2 inhibitors (SGLT2i) [11].</p> <p>A comparison of Medicare expenditures and resource use between HFrEF patients treated with Entresto vs. patients treated with ACEi/ARBs and those who received neither Entresto nor ACEi/ARB was conducted from an accountable care organization perspective [12]. The patient groups were matched as well as controlled for treatment adherence (proportion of days covered <math>\geq 80\%</math>) [12]. Patients treated with Entresto had a mean annual medical cost that was \$875 less than the ACEi/ARBs group and \$9,369 less than the patient group receiving neither Entresto nor ACEi/ARB. Mean annual rehospitalization and skilled nursing facility (SNF) costs for patients who received Entresto were \$1,778 and \$259 less, respectively, compared to those who received ACEi/ARBs [12]. Similar analyses were conducted for beneficiaries with HFrEF within the Medicare bundled payment for care improvement (BPCI) initiative model [12]. Those treated with Entresto had lower mean congestive HF episode costs compared to the ACEi/ARBs group (\$447 less) and neither treatment group (\$10,249 less) [12]. Mean 90-day congestive HF episode rehospitalization and SNF costs were \$741 and \$298 less in the Entresto group compared to the ACEi/ARBs group, respectively [12].</p> |



| Question | Sub-Question   | Response  |
|----------|--|---|
|          |  | <p>To understand the financial impact of adopting Entresto for health systems under alternative payment models (Medicare Shared Savings Plan, BPCI initiative, and Hospital Readmission Reduction Program), a decision tree model was created to assess Entresto in the treatment of patients with acute decompensated HF (ADHF) [13]. Assuming a panel size of 100,000 patients, results showed that utilization of Entresto reduced re-hospitalization by 46.3% in patients younger than 65 and 23.4% in patients 65 years or older [13]. The overall savings associated with the adoption of Entresto were \$740 per-ADHF case per-year [13].</p> <p>The totality of evidence from these studies shows that Entresto is effective in reducing hospitalizations and post-acute care services in both Medicare Advantage and traditional Medicare FFS beneficiaries, translating into significant medical cost savings for the Medicare program.</p> <p>TAKE-AWAY: Entresto use is associated with reduced utilization of hospital and post-acute care services in patients with HFrEF, resulting in lower Medicare expenditures for Part A &amp; B services.</p> <p>ENTRESTO IS INDICATED FOR SYMPTOMATIC HEART FAILURE WITH SYSTEMIC LEFT VENTRICULAR SYSTOLIC DYSFUNCTION IN PEDIATRIC PATIENTS AGED ONE YEAR AND OLDER:</p> <p>The burden of pediatric HF is high as children whose hospitalization is complicated by HF can have more than a 20-fold increase in the risk of death [14; 15]. The 52-week Phase 3 PANORAMA-HF trial was the largest pediatric heart failure study ever conducted; however, its number of subjects was quite small compared to adult clinical trials given the rarity of HF in a pediatric population. It compared treatment with Entresto to enalapril, demonstrating a numerically greater reduction in NT-proBNP from baseline, 44% vs. 33%, with Entresto compared to enalapril, respectively [16; 17]. While the between-group difference was not statistically significant, the reductions for Entresto and enalapril were similar or greater in magnitude when compared to adult trials.</p> <p>TAKE-AWAY: Entresto treatment of pediatric HF is especially important, given that up to 33% of all pediatric cardiac admissions are related to HF, and children whose hospitalization is complicated by HF can have a significantly increased risk of death.</p> |
|          | Hyperlink to Citation - Additional Materials for Question 29 | <div style="background-color: black; height: 20px; width: 100%;"></div>   |





| Question  | Sub-Question  | Response  |
|---|---|---|
|   | Hyperlink to Table/Charts/Graphs - Additional Materials for Question 29 |   |
|   | Evidence Submitted include a cost-effectiveness measure?                | N   |
|   | What type of Evidence is shown?   |   |
| Question 30:<br>Addressing<br>Unmet<br>Medical<br>Needs | Response to Question 30   | <p>ENTRESTO ADDRESSES AN UNMET NEED FOR CHRONIC HEART FAILURE PATIENTS BY DEMONSTRATING SUPERIORITY TO FORMER STANDARD OF CARE ANGIOTENSIN-CONVERTING ENZYME INHIBITORS (ACEi) and ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs) IN REDUCING DEATH, AND HOSPITALIZATIONS:</p> <p>The Food and Drug Administration (FDA) Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics (May 2014) considers a new therapy to address an unmet medical need if the treatment “has an improved effect on a serious outcome(s) . . . compared with available therapy (e.g., superiority of the new drug to available therapy when either used alone or in combination with available therapy (i.e., as demonstrated in an add-on study)).” Entresto has proven through multiple clinical trials, detailed in responses to questions 27-29, to be superior to the former standard of care ACEi/ARBs in reducing the most serious outcome of death in addition to helping adult chronic heart failure (CHF) patients stay out of the hospital.</p> <p>HF IMPOSES SIGNIFICANT CLINICAL, QUALITY OF LIFE, AND ECONOMIC BURDENS FOR HEART FAILURE PATIENTS COVERED BY MEDICARE:</p> <p>The prevalence of heart failure (HF) is rising in the United States (US), partly due to improved survival among patients experiencing a myocardial infarction (MI), as many survivors develop HF [1]. Almost 7 million Americans are currently living with CHF, according to the National Center for Health Services [2]. Although several risk factors for HF are prevalent in the general population (e.g., hypertension, diabetes mellitus) [1], there is a disproportionate clinical burden of HF in the Medicare population, including a trend of increasing 30-day mortality rates. [3; 4]. Older adults have a higher risk of developing and dying from HF, with evidence showing that older adults with a diagnosis of HF</p> |



| Question | Sub-Question | Response   |
|----------|--------------|--|
|          |              | <p>have a 5-year mortality that approaches 50% [5]. HF is also shown to be the leading cause of hospitalization for older Americans. The CMS Chronic Conditions Data Warehouse indicated that 14.5% of Medicare Fee for Service (FFS) beneficiaries had a HF diagnosis in 2018 [6], with CHF Medicare beneficiaries having the highest readmission rate [5].</p> <p>Frequent HF hospitalizations impose a significant burden on the healthcare system. In 2014, there were approximately 1.1 million emergency department (ED) visits, 980,000 hospitalizations, and 84,000 deaths from primary HF [3]. Considering comorbid HF, these numbers substantially increased; 4.1 million ED visits, 3.4 million hospitalizations, and 231,000 deaths [3].</p> <p>HF significantly reduces health related quality of life (HRQoL). A 2009 study found that among patients with HF, 39% had depressive symptoms and 21% had severe depression after hospitalization [7]. Several studies have demonstrated that poor HRQoL after hospital discharge was a predictor of rehospitalization and mortality [8; 7; 9]. A 2008 study of 84 patients found that after hospital discharge, 70% had depression and anxiety, indicating a poorer HRQoL versus the general population [10].</p> <p>Alongside disease burden, patients with HF experience significant economic burden. From 2012 to 2030, total direct costs of HF are expected to increase from \$21 billion to \$53 billion [11]. Moreover, the cost of HF in the US is projected to grow to \$69.8 billion by 2030, with hospital admissions as the largest driver of direct medical costs [5]. Costs associated with hospitalizations are mostly incurred through Medicare [3].</p> <p>ENTRESTO IS WELL-POSITIONED TO ADDRESS SEVERAL UNMET NEEDS RELATED TO MEDICARE PATIENTS WITH HF:</p> <p>Entresto has been shown to significantly reduce cardiovascular death and HF hospitalizations in adult patients with left ventricular ejection fraction (LVEF) below normal in landmark head-to-head clinical trials, PARADIGM-HF, PIONEER-HF &amp; PARAGON-HF. Entresto has also proved to be effective in reducing HF symptoms, physical and social functioning and quality of life for heart failure with reduced ejection fraction (HFrEF) patients [12-14].</p> <p>Entresto is shown to be an effective treatment in relieving the clinical burden of CHF among Medicare beneficiaries by providing a significant improvement in mortality. In a cohort of older CHF Medicare patients, Entresto treated patients had an 18% lower mortality risk compared to patients taking ACEi/ARBs [15]. An analysis by Fonarow et al showed that the use of Entresto in eligible HFrEF patients was estimated to prevent 28,484 deaths a year [16]. Patients who receive Entresto also reported significant improvements in their HRQoL [13; 12]. Moreover, the use of Entresto can provide significant cost savings when compared to ACEi/ARBs [17-20].</p> <p>Prior to the FDA approval of Entresto, ACEi/ARBs were the standard of care for adults with CHF. Following the entry of</p> |



| Question | Sub-Question  | Response   |
|----------|---|--|
|          |   | <p>Entresto, treatment guidelines recommended that patients who tolerate an ACEi or ARB be switched to Entresto to further reduce morbidity and mortality [1; 21-23]. The most recent 2022 HF Treatment guideline upgraded the recommendation for Entresto to be the first-choice renin-angiotensin system inhibitor (RASi) in HFrEF, and recommends Entresto be initiated in hospitalized patients with acute HFrEF before discharge in the absence of contraindications [23].</p> <p>The use of quadruple therapy (angiotensin receptor-neprilysin inhibitor [ARNi], sodium-glucose cotransporter-2 inhibitors, mineralocorticoid receptor antagonists and evidence-based beta blockers) is recommended by HF treatment guidelines due to the complementary benefits of these medications [23]. Entresto is the only medication which was directly tested versus ACEi for the treatment of patients with HFrEF and versus ARB in the treatment of patients with heart failure with preserved ejection fraction.</p> <p>TAKE-AWAY: Entresto is an essential and irreplaceable medication for the treatment of patients CHF with LVEF less than normal and addresses several unmet needs in the Medicare population.</p> <p>In conclusion, there is no therapeutic alternative to Entresto, the first-and-only ARNi approved in the US for the treatment of CHF patients with LVEF below normal. It is the only therapy that has demonstrated clinical superiority versus ACEi/ARBs, the former standard of care, in reducing mortality, morbidity, and hospitalizations in adult patients with CHF and LVEF less than normal. Alongside its clinical superiority, Entresto significantly improves HRQoL for patients with HFrEF and treatment with Entresto instead of an ACEi reduces medical costs and provides high economic value, as per the 2022 HF treatment guidelines. Through these clinical advances, Entresto addresses the unmet medical need for CHF patients with LVEF less than normal.</p> |
|          | Hyperlink to Citation - Additional Materials for Question 30            | <div></div>  |
|          | Hyperlink to Table/Charts/Graphs - Additional Materials for Question 30 | <div></div>  |

Manufacturer E2 Submissions – Novartis



| Question   | Sub-Question   | Response   |
|--|--|--|
|  | Evidence Submitted include a cost-effectiveness measure? | N  |
|  | What type of Evidence is shown?                          |  |
| Question 31:<br>Patient and Caregiver Experience | Response to Question 31                                  |  |
| Question 32:<br>Executive Summary                | Response to Question 32                                  | <p>Almost 7 million Americans are currently living with chronic heart failure (CHF), a progressive chronic condition that can lead to hospitalization or shortened life expectancy. Heart failure (HF) is characterized by the heart's inability to efficiently pump blood throughout the body. Insufficient blood flow to vital organs (e.g., lungs) leads to worsening symptoms and increased risk of life-threatening complications and death. HF prevalence is on the rise and is expected to increase by 46% by 2030, disproportionately impacting Medicare beneficiaries.</p> <p>Entresto® (sacubitril/valsartan) is the first and only angiotensin receptor-neprilysin inhibitor (ARNI) indicated to reduce the risk of cardiovascular death and hospitalization for HF in adults with CHF; benefits most clearly evident in patients with a left ventricular ejection fraction (LVEF) less than normal. Additionally, Entresto is approved for the treatment of symptomatic HF with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older.</p> <p>Entresto is part of the renin-angiotensin system inhibitors (RASi) category of medications, which include angiotensin converting enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB). However, Entresto is more than a legacy RASi because it contains two active moieties that target complementary pathways (valsartan which targets the renin-angiotensin system [RAS] and sacubitril which targets the natriuretic peptide pathway). The older ACEi/ARB classes help control blood pressure and the amount of fluid in the body, but Entresto, by targeting both pathways, relaxes blood vessels, improves blood flow, and reduces the stress and overactivation of the heart (i.e., Entresto boosts the body's innate systems to put itself back into balance). A component of Entresto, sacubitril, is not available on the market as a standalone medication and is the only neprilysin inhibitor available for HF patients. Entresto is designed</p> |

| Question | Sub-Question | Response   |
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|          |              | <p>specifically to offset the dysregulated pathophysiology of HF for CHF patients.</p> <p>The 2022 HF treatment guideline, which is the most updated guideline endorsed by the three major cardiovascular societies, recommends use of quadruple therapy for the treatment of patients with HF with reduced ejection fraction (HFrEF), which accounts for approximately 90% of all Entresto patients. These four medication classes include: ARNI (Entresto), sodium-glucose cotransporter-2 inhibitors, mineralocorticoid receptor antagonists, and evidence-based beta-blockers. All four drug classes are non-overlapping in their mechanisms of action, non-interchangeable, and additive in their clinical benefits for HFrEF patients. These four classes have received the highest recommendation, Class IA, by the guideline and are meant to be used together. In the ARNI class, the 2022 guideline names Entresto as the first-choice medication and recommends that HFrEF patients currently on an ACEi/ARB, be switched to Entresto. Multiple clinical studies have established the efficacy of Entresto.</p> <ul style="list-style-type: none"> <li>• PARADIGM-HF, one of the largest heart failure trials conducted, demonstrated that Entresto reduced the risk of cardiovascular death and hospitalization by 20% compared to enalapril (an ACEi) in HFrEF patients. The results from this trial led to the FDA approval of Entresto in 2015.</li> <li>• PIONEER-HF established that Entresto can be safely and effectively initiated in HFrEF patients hospitalized with acute decompensated HF. The results showed a superior reduction in N-terminal pro b-type natriuretic peptide (NT-proBNP) and in a post-hoc analysis demonstrated a 44% risk reduction for re-hospitalizations in Entresto treated patients compared to enalapril (an ACEi).</li> <li>• PARAGON-HF, which narrowly missed the primary endpoint, showed in a subgroup of patients with a LVEF <math>\leq</math> 57%, Entresto demonstrated a superior reduction in hospitalizations compared to valsartan (an ARB). These results led to Entresto's expanded FDA approved label for use in all CHF patients with a LVEF less than normal.</li> </ul> <p>The results from these trials and others established Entresto as a first-in-class HF therapy.</p> <p>Entresto addresses significant unmet needs in vulnerable patient populations living with CHF.</p> <ul style="list-style-type: none"> <li>• MEDICARE POPULATIONS: The therapeutic benefits of Entresto are consistently seen in real-world evidence studies that included elderly and frail patients with multiple comorbidities.</li> <li>• RACIAL MINORITIES: Entresto improves patient outcomes regardless of racial/ethnic background.</li> <li>• CHILDREN: In patients aged one year and older, Entresto is one of the few FDA approved therapies for treatment of symptomatic HF with systemic left ventricular systolic dysfunction. When considering the value of a medication, the total cost of care, inclusive of both medical and pharmacy costs, should be considered. Entresto has been proven in multiple real-world studies to reduce medical costs.</li> </ul> |

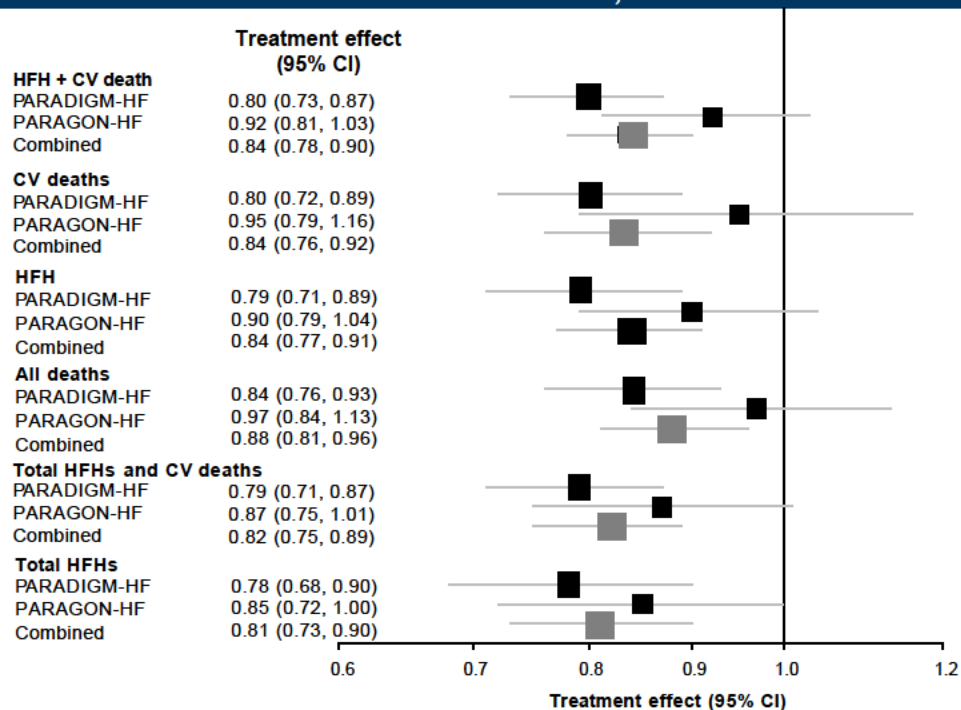




| Question | Sub-Question | Response  |
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|          |              | <p>1. Following the label expansion of Entresto in 2021, a study of 7,658 Medicare Advantage patients with CHF showed that treatment with Entresto lowered all-cause medical costs by \$4,959 over 12-months compared to the 12-month period prior to Entresto initiation.</p> <p>2. Albert et al. showed that the medical cost savings associated with Entresto compared to patients taking ACEi/ARBs fully offset the additional medication cost of Entresto (\$1,275 net savings Per Member Per Month; 75% of the patients were enrolled in a Medicare Advantage plan.</p> <p>3. Prime Therapeutics published a study, among their commercially insured population, that showed a \$10,177 (or 22%) annual total cost of care reduction among HFrEF patients newly initiating Entresto. The medical savings fully offset the cost of Entresto.</p> <p>In addition to the evidence-based clinical superiority and real-world medical cost savings, Entresto improves symptoms, physical and social functioning, and quality of life outcomes for CHF patients. While other medications, such as ACEi/ARBs had historically been used to manage patients with CHF, none have demonstrated the same level of death and hospitalization reductions as Entresto for patients with a LVEF less than normal. The totality of evidence supporting Entresto has resulted in the 2022 HF guideline stating that “in patients with chronic symptomatic HFrEF, treatment with an ARNI (Entresto) instead of an ACEi provides high economic value.”The Food and Drug Administration Guidance for Industry Expediated Programs for Serious Conditions–Drugs and Biologics (May 2014) defines “unmet medical need” as including a treatment that “has an improved effect on a serious outcome(s). compared with available therapy”.Entresto meets this definition through proven superiority to the former standard of care ACEi/ARBs in reducing the most serious outcome of death, in addition to helping adult CHF patients with a LVEF less than normal stay out of the hospital.</p> |

**FIGURE 1: Treatment effects of Entresto vs. Active comparator (enalapril or valsartan) in the pooled cohort of PARADIGM-HF and PARAGON-HF. Adapted with permission from Solomon SD et al.**

**Hazard ratios<sup>a</sup> and rate ratios<sup>b</sup> for events in the PARADIGM-HF, PARAGON-HF and the overall pooled cohort**



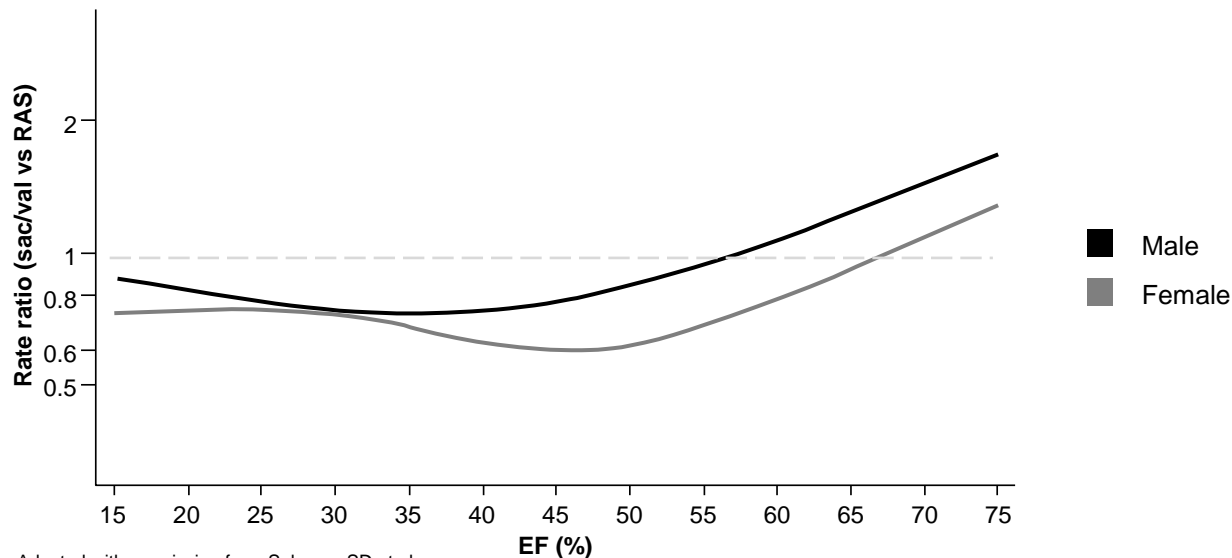
Adapted with permission from Solomon SD et al.

CV, cardiovascular; HFH, heart failure hospitalization.

<sup>a</sup>For first occurrence of CV death or HFH, CV death, first occurrence of heart failure hospitalization, all-cause mortality; <sup>b</sup>For total HFHs and CV death, and total HFHs. Solomon SD et al. *Circulation*. 2020;141:352-361.

**FIGURE 2: Treatment effects of Entresto vs. active comparator (enalapril or valsartan) across the spectrum of LVEF for the composite outcome of total HF hospitalizations and CV death stratified by sex. Adapted with permission from Solomon SD et al.**

**Continuous treatment effects of sac/val vs active comparator (either enalapril or valsartan) by sex**

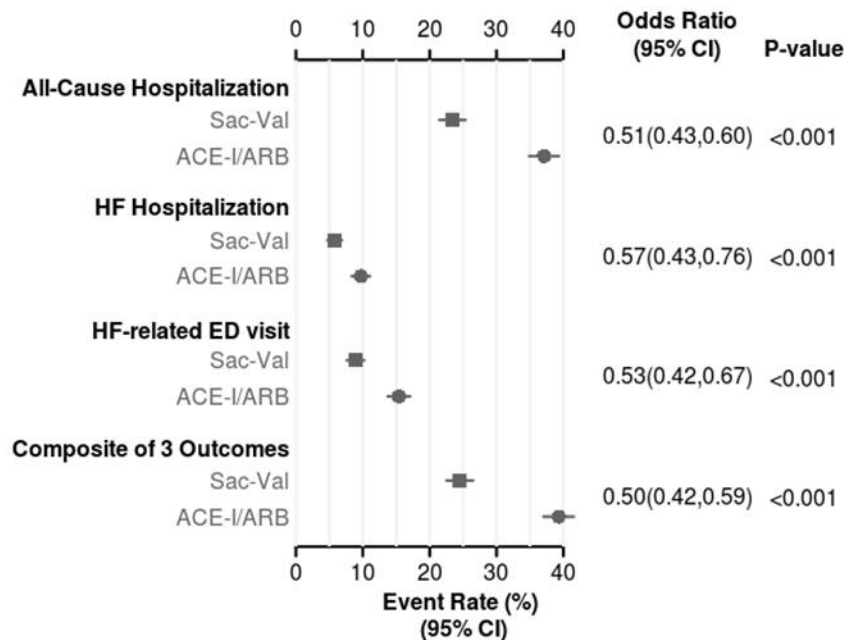


Adapted with permission from Solomon SD et al.

- The effect modification by LVEF on efficacy of sac/val was similar in both men and women, but the benefit persisted to higher EF in women compared with men (3-way interaction  $P=.032$ )
- While NT-proBNP varied by both sex and EF, in a comprehensive model incorporating treatment by NT-proBNP interaction terms with treatment-by-sex and treatment-by-EF interaction terms, only sex and EF remained significant.

**FIGURE 3: Healthcare resource use in HF patients with LVEF below normal treated with Entresto vs. ACEi/ARB in a multi-state healthcare system. (Novartis Data on File)**

**Healthcare Resource Use in HF Patients with LVEF Below Normal Treated with Entresto vs. ACEi/ ARB**



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### Question 30

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**Public E2 Submission**

IPAY: 2026



| Question                                   | Sub-Question   | Response   |
|--|--|--|
| Question 26:<br>Respondent<br>Information  | Selected Drug  | VALSARTAN SACUBITRILAT   |
|  | Q26 - Respondent Name  |  |
|  | Q26 - Organization Name<br>(if applicable)                     | AAHFN  |
|  | Respondent Email   |  |
| Question 27:<br>Prescribing<br>Information | Who is completing this<br>form?                                | PAO  |
|  | Prescribing Information  | <p>The medication Entresto has been approved by the FDA for the treatment of chronic heart failure. Entresto is also recommended by the American Heart Association, American College of Cardiology, and the Heart Failure Society of America as a class 1a recommendation for patients with heart failure with reduced ejection fraction and New York Heart Association Class 2 to 3 symptoms as best practice to reduce morbidity and mortality. It is also a class 1a recommendation in patients with chronic heart failure with reduced ejection fraction currently using a therapeutic alternative such as an ACE-I or ARB to switch the patient to Entresto if feasible (AHA/ACC, 2022)..Entresto works to inhibit the renin-angiotensin system and reduces morbidity and mortality for patients with heart failure. Entresto is also recommended in the treatment of de novo heart failure in the acute care setting because this medication is found to improve health status, reduce the prognostic biomarker NT-proBNP, and improve left ventricular remodeling parameters compared to its therapeutic alternatives ACE-I and ARB. Entresto is found to reduce the risk of cardiovascular death or heart failure hospitalization in the heart failure patient population by 20% compared to ACE-I. Other trials have found that Entresto is found to reduce NT-proBNP levels without the side effects of worsening renal function or hyperkalemia compared to ACE-I (AHA/ACC, 2022). .Given the importance of Entresto in guideline-directed medical therapy for heart failure patients with known benefits of reduction in mortality and heart failure hospitalization and improved left ventricular remodeling, it is clear that Entresto is an essential medication in treating heart failure patients. We urge this committee to consider the benefit Entresto has shown for the heart failure population and lower the price of this important and necessary medication so that the benefits can be reaped for all patients.</p> |
|  | Evidence Submitted include<br>a cost-effectiveness<br>measure? | D  |
|  | What type of Evidence is<br>shown?                             |  |



## Public E2 Submission

IPAY: 2026



| Question | Sub-Question | Response |
|----------|--------------|----------|
|----------|--------------|----------|

|   |   |   |
|---|---|---|
| Question 28:<br>Therapeutic<br>Impact and<br>Comparative<br>Effectiveness | Therapeutic Impact and<br>Comparative Effectiveness | <b>Response</b><br>Entresto (sacubitril/valsartan) is a medication used for the treatment of heart failure with reduced ejection fraction (HFrEF). It is a newer drug that has shown significant therapeutic benefits in clinical trials compared to existing therapeutic alternatives.. <ul style="list-style-type: none"><li>• Mechanism of Action: Entresto combines two active ingredients, sacubitril and valsartan. Sacubitril inhibits neprilysin, an enzyme that breaks down beneficial peptides in the heart. Valsartan is an angiotensin receptor blocker (ARB) that helps relax blood vessels. This combination addresses both neurohormonal pathways involved in heart failure.</li><li>• Improved Outcomes: The PARADIGM-HF trial has demonstrated that Entresto is superior to enalapril in reducing the risk of cardiovascular death and hospitalization for heart failure in patients with HFrEF. This has led to its widespread adoption in the treatment of HFrEF.</li><li>• Reduction in Mortality: Entresto has been shown to significantly reduce the risk of cardiovascular death compared to enalapril. It is part of the guideline therapy in heart failure management due to its potential to prolong life in HFrEF patients.</li><li>• Symptom Management: Patients on Entresto often experience improved symptom management like reduced fatigue, decreased shortness of breath, and decreased edema. This can help improve a patient's quality of life.</li><li>• Tolerability: In general, Entresto is well-tolerated by most patients. It has a side effect profile similar to that of other ACE inhibitors or ARBs. However, it still requires regular monitoring in order to make sure kidney function and electrolytes are in normal limits.</li><li>• Combination Therapy: Entresto is often used in combination with other guideline medical therapy for heart failure such as beta-blockers, mineralocorticoid receptor antagonists (MRAs), and SGLT2 inhibitors to achieve optimal therapeutic benefits.</li><li>• Individualized Treatment: The choice between Entresto and other heart failure medications is typically based on individual patient factors. These include disease severity, tolerability, and contraindications. Not all patients are candidates for Entresto, and some may benefit more from traditional ACE inhibitors or ARBs.</li></ul> |
|---|---|---|

Hyperlink to  
Table/Charts/Graphs -  
Additional Materials for  
Question 28  
Evidence Submitted include  
a cost-effectiveness  
measure?

## Public E2 Submission

IPAY: 2026



| Question  | Sub-Question                    | Response   |
|---|---------------------------------|--|
|   | What type of Evidence is shown? |  |
| Question 29:<br>Comparative Effectiveness on Specific Populations | Response to Question 29         | <p>Questions on Comparative Effectiveness on Specific Populations:</p> <ul style="list-style-type: none"><li>• What is known about the comparative effectiveness of the selected drug and therapeutic alternatives to the selected drug with respect to specific populations, such as individuals with disabilities, the elderly, individuals who are terminally ill, and children? Entresto is not approved for children.</li><li>• Are there other specific populations not noted in the question above that use the selected drug that could be considered? YES If so, please explain..Pregnancy: Do not use. This medication may be harmful to an unborn child..Lactation: Consult a doctor before using.Alcohol: Limit intake while taking this medication.Dosing adjustments are needed for severe renal impairment (eGFR &lt;30 mL/min/1.73 m2) or moderate hepatic impairment (Child-Pugh B classification)</li></ul> <p>ENTRESTO has been associated with a higher rate of angioedema in Black patients .Should not be prescribed for anyone with history of angioedema.</p> <ul style="list-style-type: none"><li>• As applicable, for other specific populations that use the selected drug, what is known about comparative effectiveness of the selected drug and its therapeutic alternative(s)?</li><li>• What health equity considerations should CMS consider related to specific populations taking the selected drugs? No known specific considerations for specific populations. This may include, but is not limited to, challenges or advantages accessing the drug compared to therapeutic alternatives, differences in clinical or other outcomes, or differences in disease or condition symptoms for a specific population that the drug does or does not adequately address. .A challenge for many populations is cost, depending on insurance coverage.</li></ul> <p>Entresto is supported by the 2022 Heart Failure Guideline, as a first-line treatment and to replace well-tolerated ACEi/ARB in patients with HFrEF. ENTRESTO was also included as a treatment option for HFmrEF (LVEF 41%-49%) and selected patients with HFpEF (LVEF ≥50%), particularly for patients with LVEF on the lower end of these spectrums.*In PARAGON-HF, defined as LVEF ≥45% with structural heart disease (LAE or LVH); median LVEF was 57%.</p> <ul style="list-style-type: none"><li>• In addition to comparative effectiveness, please discuss any differences in the safety profile of the selected drug compared to its therapeutic alternative(s) for each applicable specific population. No additional information.</li></ul> |

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| Question  | Sub-Question   | Response   |
|---|--|--|
|   | Hyperlink to Citation -<br>Additional Materials for<br>Question 29               |  |
|   | Hyperlink to<br>Table/Charts/Graphs -<br>Additional Materials for<br>Question 29 |  |
|   | Evidence Submitted include<br>a cost-effectiveness<br>measure?                   |  |
|   | What type of Evidence is<br>shown?   |  |
| Question 30:<br>Addressing<br>Unmet<br>Medical<br>Needs | Response to Question 30  |  |
|   | Hyperlink to Citation -<br>Additional Materials for<br>Question 30               | American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines.<br>2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. |
|   | Hyperlink to<br>Table/Charts/Graphs -<br>Additional Materials for<br>Question 30 |  |
|   | Evidence Submitted include<br>a cost-effectiveness<br>measure?                   |  |
|   | What type of Evidence is<br>shown?   |  |

# Public E2 Submission

IPAY: 2026



| Question   | Sub-Question            | Response |
|--|-------------------------|----------|
| Question 31:<br>Patient and<br>Caregiver<br>Experience | Response to Question 31 |          |
| Question 32:<br>Executive<br>Summary                   | Response to Question 32 |          |





**Public E2 Submission**

IPAY: 2026



| Question  | Sub-Question   | Response               |
|---|--|------------------------|
| Question 26:<br>Respondent<br>Information                                 | Selected Drug  | VALSARTAN SACUBITRILAT |
|   | Q26 - Respondent Name  |                        |
|   | Q26 - Organization Name<br>(if applicable)                                       | AARP                   |
|   | Respondent Email   |                        |
|   | Who is completing this<br>form?  | PAT                    |
| Question 27:<br>Prescribing<br>Information                                | Prescribing Information  |                        |
|   | Evidence Submitted include<br>a cost-effectiveness<br>measure?                   |                        |
|   | What type of Evidence is<br>shown?   |                        |
| Question 28:<br>Therapeutic<br>Impact and<br>Comparative<br>Effectiveness | Therapeutic Impact and<br>Comparative Effectiveness                              |                        |
|   | Hyperlink to<br>Table/Charts/Graphs -<br>Additional Materials for<br>Question 28 |                        |
|   | Evidence Submitted include<br>a cost-effectiveness<br>measure?                   |                        |
|   | What type of Evidence is<br>shown?   |                        |
|   | Response to Question 29  |                        |

## Public E2 Submission

IPAY: 2026



| Question   | Sub-Question   | Response |
|--|--|----------|
| Question 29:<br>Comparative<br>Effectiveness<br>on Specific<br>Populations | Hyperlink to Citation -<br>Additional Materials for<br>Question 29               |          |
|  | Hyperlink to<br>Table/Charts/Graphs -<br>Additional Materials for<br>Question 29 |          |
|  | Evidence Submitted include<br>a cost-effectiveness<br>measure?                   |          |
|  | What type of Evidence is<br>shown?   |          |
| Question 30:<br>Addressing<br>Unmet<br>Medical<br>Needs                    | Response to Question 30  |          |
|  | Hyperlink to Citation -<br>Additional Materials for<br>Question 30               |          |
|  | Hyperlink to<br>Table/Charts/Graphs -<br>Additional Materials for<br>Question 30 |          |
|  | Evidence Submitted include<br>a cost-effectiveness<br>measure?                   |          |
|  | What type of Evidence is<br>shown?   |          |

## Public E2 Submission

IPAY: 2026



| Question | Sub-Question | Response |
|----------|--------------|----------|
|----------|--------------|----------|

|  |                         |  |
|--|-------------------------|--|
| Question 31:<br>Patient and<br>Caregiver<br>Experience | Response to Question 31 | <p><b>Response</b></p> <p>AARP, which advocates for the more than 100 million Americans age 50 and over, is pleased to submit the following comments in response to the Centers for Medicare and Medicaid Services' (CMS) Medicare Drug Price Negotiation Program Patient-Focused Listening Sessions. AARP commends CMS for soliciting feedback from the public and appreciates its efforts to ensure that patients, caregivers, and health care providers have a voice in the negotiation process. ..Data shows that brand-name drug prices have increased dramatically faster than inflation for decades. List prices for the 25 brand-name drugs with the highest total Medicare Part D spending in 2021 have increased by an average of 226% - or more than tripled - since they first entered the market. Data also shows that all but one of the top 25 drugs' lifetime price increases greatly exceeded the corresponding annual rate of general inflation (Consumer Price Index All Urban Consumers for All Items; CPI-U) over the period that each product has been on the market (i.e., product launch date until May 2023). For example, the price of Enbrel (Etanercept), used to treat rheumatoid arthritis and psoriatic arthritis, has increased by 701% since coming to market in 1998, and the price of Januvia (Sitagliptin), used to treat diabetes, has increased by 275% since entering the market in 2006. Further, the median price of a new brand-name prescription drug is now approximately \$200,000 per year, so even relatively small percentage price increases can translate into thousands of dollars and put life-saving medications out of reach of the patients who need them...High prescription drug prices and related out-of-pocket costs can negatively affect older adults' health and financial security. Too many seniors are being forced spend down their retirement savings or to choose between paying for their prescription drugs or other important needs like groceries or housing. It is virtually impossible to adequately prepare for your future health care costs when they include prescription drugs with prices that are set on the basis of what the market will bear. ..Successful implementation of the new federal law will help reduce prescription drug prices and costs and ensure that millions of older Americans are better able to access the prescription drugs they need at a price they can afford. The Medicare drug price negotiation process will also finally allow CMS to push back on indiscriminately escalating drug prices and ensure that taxpayer funds are paying for value – all while saving billions for Medicare and its beneficiaries. The CBO estimates that the Negotiation Program will save Medicare and the American taxpayers nearly \$98.5 billion over 10 years, reduce the budget deficit by \$25 billion in 2031, and save Medicare Part D enrollees \$7 billion in 2031 due to lower out-of-pocket costs and premiums. ..This is about real people whose lives are on the line. For decades, older Americans have paid the highest prices in the world for prescription drugs - often three times higher than people in other countries. Now is the time to change that. Effective implementation of this Program will represent a major victory for older Americans and their families across the country who are struggling to afford their prescriptions. It will also help encourage and appropriately reward the development of truly innovative products. AARP stands ready to assist in any way with these and other efforts to bring down drug prices and help older Americans afford the medications and treatments they need. If you have any questions, please do not hesitate to contact me or Gidget Benitez at <a href="mailto:gbenitez@aarp.org">gbenitez@aarp.org</a>...Sincerely, ..Nancy LeaMond.Executive Vice President and Chief Advocacy &amp; Engagement Officer</p> |
|--|-------------------------|--|

# Public E2 Submission

IPAY: 2026



| Question | Sub-Question | Response |
|----------|--------------|----------|
|----------|--------------|----------|

|                                      |                         |  |
|--------------------------------------|-------------------------|--|
| Question 32:<br>Executive<br>Summary | Response to Question 32 |  |
|--------------------------------------|-------------------------|--|







October 2, 2023

Meena Seshamani, M.D., Ph.D.  
Director, Center for Medicare  
Centers for Medicare & Medicaid Services  
U.S. Department of Health and Human Services

Dear Dr. Seshamani:

AARP, which advocates for the more than 100 million Americans age 50 and over, is pleased to submit the following comments in response to the Centers for Medicare and Medicaid Services' (CMS) Medicare Drug Price Negotiation Program Patient-Focused Listening Sessions. AARP commends CMS for soliciting feedback from the public and appreciates its efforts to ensure that patients, caregivers, and health care providers have a voice in the negotiation process.

Data shows that brand-name drug prices have increased dramatically faster than inflation for decades. List prices for the 25 brand-name drugs with the highest total Medicare Part D spending in 2021 have increased by an average of 226%—or more than tripled—since they first entered the market.<sup>1</sup> Data also shows that all but one of the top 25 drugs' lifetime price increases greatly exceeded the corresponding annual rate of general inflation (Consumer Price Index All Urban Consumers for All Items; CPI-U) over the period that each product has been on the market (i.e., product launch date until May 2023).<sup>2</sup> For example, the price of Enbrel (Etanercept), used to treat rheumatoid arthritis and psoriatic arthritis, has increased by 701% since coming to market in 1998, and the price of Januvia (Sitagliptin), used to treat diabetes, has increased by 275% since entering the market in 2006.<sup>3</sup> Further, the median price of a new brand-name prescription drug is now approximately \$200,000 per year,<sup>4</sup> so even relatively small percentage price increases can translate into thousands of dollars and put life-saving medications out of reach of the patients who need them.

High prescription drug prices and related out-of-pocket costs can negatively affect older adults' health and financial security. Too many seniors are being forced spend down their retirement savings or to choose between paying for their prescription drugs or other important needs like groceries or housing. It is virtually impossible to adequately prepare for your future health care costs when they include prescription drugs with prices that are set on the basis of what the market will bear.

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<sup>1</sup> Leigh Purvis, "Prices for Top Medicare Part D Drugs Have More Than Tripled Since Entering the Market." Washington, DC: AARP Public Policy Institute, August 10, 2023. <https://doi.org/10.26419/ppi.00202.001>.

<sup>2</sup> *Id.*

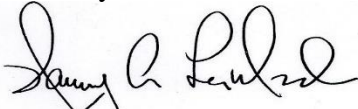
<sup>3</sup> *Id.*

<sup>4</sup> Benjamin N. Rome, Alexander C. Egilman, and Aaron S. Kesselheim, "Trends in Prescription Drug Launch Prices, 2008– 2021," *Journal of the American Medical Association* 327, no. 21 (2022): 2145–47, <https://jamanetwork.com/journals/jama/fullarticle/2792986>; Deena Beasley, "U.S. New Drug Price Exceeds \$200,000 Median in 2022," *Reuters*, January 5, 2023, <https://www.reuters.com/business/healthcare-pharmaceuticals/us-new-drug-price-exceeds-200000-median-2022-2023-01-05/>.

Successful implementation of the new federal law will help reduce prescription drug prices and costs and ensure that millions of older Americans are better able to access the prescription drugs they need at a price they can afford. The Medicare drug price negotiation process will also finally allow CMS to push back on indiscriminately escalating drug prices and ensure that taxpayer funds are paying for value – all while saving billions for Medicare and its beneficiaries. The CBO estimates that the Negotiation Program will save Medicare and the American taxpayers nearly \$98.5 billion over 10 years,<sup>5</sup> reduce the budget deficit by \$25 billion in 2031,<sup>6</sup> and save Medicare Part D enrollees \$7 billion in 2031 due to lower out-of-pocket costs and premiums.<sup>7</sup>

This is about real people whose lives are on the line. For decades, older Americans have paid the highest prices in the world for prescription drugs - often three times higher than people in other countries. Now is the time to change that. Effective implementation of this Program will represent a major victory for older Americans and their families across the country who are struggling to afford their prescriptions. It will also help encourage and appropriately reward the development of truly innovative products. AARP stands ready to assist in any way with these and other efforts to bring down drug prices and help older Americans afford the medications and treatments they need. If you have any questions, please do not hesitate to contact me or Gidget Benitez at [gbenitez@aarp.org](mailto:gbenitez@aarp.org).

Sincerely,



Nancy A. LeaMond  
Executive Vice President and  
Chief Advocacy & Engagement Officer

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<sup>5</sup> Congressional Budget Office, “Estimated Budgetary Effects of Public Law 117-169, to Provide for Reconciliation Pursuant to Title II of S. Con. Res. 14.” [https://www.cbo.gov/system/files/2022-09/PL117-169\\_9-7-22.pdf](https://www.cbo.gov/system/files/2022-09/PL117-169_9-7-22.pdf). Accessed September 27, 2023.

<sup>6</sup> Congressional Budget Office, “How CBO Estimated the Budgetary Impact of Key Prescription Drug Provisions in the 2022 Reconciliation Act.” <https://www.cbo.gov/system/files/2023-02/58850-IRA-Drug-Provs.pdf>. Accessed September 27, 2023.

<sup>7</sup> *Id.*

**Public E2 Submission**

IPAY: 2026



| Question  | Sub-Question   | Response               |
|---|--|------------------------|
| Question 26:<br>Respondent<br>Information                                 | Selected Drug  | VALSARTAN SACUBITRILAT |
|   | Q26 - Respondent Name  |                        |
|   | Q26 - Organization Name<br>(if applicable)                                       | Aimed Alliance         |
|   | Respondent Email   |                        |
| Question 27:<br>Prescribing<br>Information                                | Who is completing this<br>form?  |                        |
|   | Prescribing Information  |                        |
|   | Evidence Submitted include<br>a cost-effectiveness<br>measure?                   |                        |
| Question 28:<br>Therapeutic<br>Impact and<br>Comparative<br>Effectiveness | What type of Evidence is<br>shown?   |                        |
|   | Therapeutic Impact and<br>Comparative Effectiveness                              |                        |
|   | Hyperlink to<br>Table/Charts/Graphs -<br>Additional Materials for<br>Question 28 |                        |
|   | Evidence Submitted include<br>a cost-effectiveness<br>measure?                   |                        |
|   | What type of Evidence is<br>shown?   |                        |
|   | Response to Question 29  |                        |

## Public E2 Submission

IPAY: 2026



| Question   | Sub-Question   | Response |
|--|--|----------|
| Question 29:<br>Comparative<br>Effectiveness<br>on Specific<br>Populations | Hyperlink to Citation -<br>Additional Materials for<br>Question 29               |          |
|  | Hyperlink to<br>Table/Charts/Graphs -<br>Additional Materials for<br>Question 29 |          |
|  | Evidence Submitted include<br>a cost-effectiveness<br>measure?                   |          |
|  | What type of Evidence is<br>shown?   |          |
| Question 30:<br>Addressing<br>Unmet<br>Medical<br>Needs                    | Response to Question 30  |          |
|  | Hyperlink to Citation -<br>Additional Materials for<br>Question 30               |          |
|  | Hyperlink to<br>Table/Charts/Graphs -<br>Additional Materials for<br>Question 30 |          |
|  | Evidence Submitted include<br>a cost-effectiveness<br>measure?                   |          |
|  | What type of Evidence is<br>shown?   |          |

# Public E2 Submission

IPAY: 2026



| Question   | Sub-Question            | Response |
|--|-------------------------|----------|
| Question 31:<br>Patient and<br>Caregiver<br>Experience | Response to Question 31 |          |
| Question 32:<br>Executive<br>Summary                   | Response to Question 32 |          |







September 28, 2023

Chiquita Brooks-LaSure  
Administrator  
U.S. Centers for Medicare & Medicaid Services  
7500 Security Boulevard  
Baltimore, MD 21244

Re: IRA Patient Listening Sessions

Dear Administrator Brooks-LaSure:

Aimed Alliance is a not-for-profit health policy organization that seeks to protect and enhance the rights of health care consumers and providers. We are writing to express our concerns with the Inflation Reduction Act's (IRA) Medicare Drug Price Negotiation Program Patient-Focused Listening Sessions.

While we support efforts aimed at making prescription drugs more affordable for Medicare Part D beneficiaries, Aimed Alliance strongly urges the Centers for Medicare & Medicaid Services (CMS) to ensure the patient voice and perspective is valued in a genuine, long-term, and sustainable manner.

## **I. Background**

In August 2022, Congress passed the IRA, which provided CMS the authority to directly negotiate the prices of certain prescription drugs with drug manufacturers.<sup>1</sup> The negotiations are limited to single source drugs, without generic or biosimilar alternatives, that have been on the market for at least 7 years, or 11 years for biologics.<sup>2</sup> On August 29, 2023, CMS published a list of 10 prescription drugs that are subject to the Medicare negotiation process. These drugs cover treatments for cardiovascular diseases, diabetes, chronic kidney disease, psoriasis, rheumatoid arthritis, psoriatic arthritis, Crohn's disease, and ulcerative colitis.<sup>3</sup> CMS stated these drugs were identified as the ten most expensive covered Part D drugs.

In determining the negotiated price CMS will impose, CMS stated it will consider various factors, including comparative effectiveness and impact on specific populations, such as individuals with disabilities, the elderly, terminally ill patients, children, and others; and the extent to which the drug and its alternatives address an unmet medical need.<sup>4</sup> Aimed Alliance urges CMS to ensure patient and provider lived experiences are adequately valued when considering these factors and throughout this process.

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<sup>1</sup> CMS, *Fact Sheet: Key Information on the Process for the First Round of Negotiations for the Medicare Drug Price Negotiation Program*, <https://www.cms.gov/files/document/fact-sheet-negotiation-process-flow.pdf>

<sup>2</sup> *Id.*; CMS, *Medicare Drug Price Negotiation Program: Selected Drugs for Initial Price Applicability Year 2026*, <https://www.cms.gov/files/document/fact-sheet-medicare-selected-drug-negotiation-list-ipay-2026.pdf>

<sup>3</sup> *Id.*

<sup>4</sup> <https://www.cms.gov/files/document/fact-sheet-medicare-selected-drug-negotiation-list-ipay-2026.pdf>

## II. Appropriately Value Patient and Provider Lived Experiences

Aimed Alliance applauds CMS for incorporating patient and provider lived experiences in the drug negotiation process. However, we urge CMS to expand the current process to ensure a wider network of patients and providers can participate, and to guarantee patient and provider voices are genuinely valued.

Internationally, several countries employ mechanisms that allow governments to negotiate drug prices with manufacturers. For example, France and Sweden base drug pricing on factors such as therapeutic value, the price of comparable treatments, and the contributions of the drug's sales to the national economy.<sup>5</sup> Sweden further incorporates ethical considerations, prioritizing those with the greatest health care needs and ensuring the process upholds and respects individual human dignity.<sup>6</sup> By valuing the needs of patients and providers, Sweden maintains an overall high health care satisfaction rate.<sup>7</sup> In contrast, the United Kingdom, which also implements a government negotiation program, has seen reports of patients being unable to access innovative treatments that may improve their condition and quality of life due to non-patient-centered valuations.<sup>8</sup> As a result of failing to appropriately value patient-perspectives on the benefits of treatments, patients in the United Kingdom also experience reduced uptake of new cancer treatments.<sup>9</sup>

Ultimately, while various systems have provided means to center patient-perspectives and lived experiences, not all systems genuinely value these insights in determining drug prices, ultimately impacting treatment accessibility. Aimed Alliance urges CMS to properly value the lived experiences of patients, providers, and caregivers, and recognize the benefits these treatments provide to consumer's health and quality of life.

## III. Expand the Number of Listening Sessions to Ensure Diverse Representation

Under the current framework, CMS offers only one listening session for each selected prescription drug, with each session lasting less than two hours and accommodating only 20 in-person speakers. Members of the public who are not selected to speak also have the option to submit written comments.<sup>10</sup> Aimed Alliance urges CMS to expand the number of listening

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<sup>5</sup> David J. Gross, Jonathan Ratner, James Perez & Sarah Glavin, *International Pharmaceutical Controls: France, Germany, Sweden, and the United Kingdom*, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4193451/#:~:text=New%20product%20prices%20emerge%20from,sales%20to%20the%20national%20economy>.

<sup>6</sup> Global Legal Rights, *Pricing & Reimbursement Laws and Regulations 2023*, <https://www.globallegalinsights.com/practice-areas/pricing-and-reimbursement-laws-and-regulations/sweden>

<sup>7</sup> Roosa Tikkanen, et al., *Sweden Scorecard*, <https://www.commonwealthfund.org/international-health-policy-center/countries/sweden>; Ketevan Kandelaki, *Patient-centeredness as a quality domain in Swedish healthcare: results from the first national surveys in difference Swedish health care setting*, <https://bmjopen.bmj.com/content/6/1/e009056>.

<sup>8</sup> Houses of Parliament: Parliamentary Office of Science & Technology, *Drug Pricing*, [https://www.parliament.uk/globalassets/documents/post/postpn\\_364\\_Drug\\_Pricing.pdf](https://www.parliament.uk/globalassets/documents/post/postpn_364_Drug_Pricing.pdf)

<sup>9</sup> *Id.*

<sup>10</sup> CMS, *Medicare Drug Price Negotiations Program Patient-Focused Listening Sessions*, <https://www.cms.gov/inflation-reduction-act-and-medicare/medicare-drug-price-negotiation-program-patient-focused-listening-sessions>

sessions to ensure patients, organizations, and caregivers have the opportunity to speak on behalf of their communities.

The 20 speakers selected to participate in each session are requested to address patients' day-to-day experiences living with their condition and under their treatment; the benefits and side effects of the treatments; patient access, adherence, and affordability; and any additional information the speaker considers significant.<sup>11</sup> While Aimerd Alliance believes this information is crucial for appropriately determining the negotiated prices, we are concerned that relying on 20 randomly selected speakers will not provide CMS with a comprehensive perspective on these medications and their benefits to patients, providers, and caregivers. We are also concerned that this random selection process could unintentionally exclude speakers who shed light on health equity, minority health, and other access issues.<sup>12</sup> Therefore, we urge CMS to expand the number of listening sessions to ensure CMS appropriately considers the broad implications and health equity considerations of these treatments; and how these price negotiations could impact access for diverse communities.

Lastly, we strongly encourage CMS to value and give due consideration to both written and spoken comments provided by patient advocacy organizations. Individuals with chronic illnesses such as multiple sclerosis and inflammatory bowel disease (IBD) frequently experience social stigma, rejection, and workplace discrimination resulting from their condition.<sup>13</sup> For instance, one study found that out of 105 patients with IBD, 84 percent reported experiencing stigma associated with their condition.<sup>14</sup> Consequently, it is critical to recognize that some individuals with chronic conditions may not feel comfortable discussing their health, treatments, and challenges openly. As a result, they often rely on advocacy organizations to share their stories, perspectives, and experiences.

#### **IV. Conclusion**

In conclusion, we sincerely appreciate the opportunity to provide feedback on the IRA process and CMS's efforts to ensure the voices of patients, providers, and caregivers are at the forefront of this process. Please contact us at [policy@aimedalliance.org](mailto:policy@aimedalliance.org) if you have any additional questions.

Sincerely,  
Ashira Vantrees  
Counsel

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<sup>11</sup> *Id.*

<sup>12</sup> Khiara Bridges, *Implicit Bias and Racial Disparities in Health Care*, [https://www.americanbar.org/groups/crsj/publications/human\\_rights\\_magazine\\_home/the-state-of-healthcare-in-the-united-states/racial-disparities-in-health-care/](https://www.americanbar.org/groups/crsj/publications/human_rights_magazine_home/the-state-of-healthcare-in-the-united-states/racial-disparities-in-health-care/)

<sup>13</sup> Valerie A Earnshaw, Diane M. Quinn & Crystall L. Park, *Anticipated stigma and quality of life among people living with chronic illnesses*, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3644808/>

<sup>14</sup> Marco Vinenzco Lenti, et al., *Stigmatization and resilience in inflammatory bowel disease patients at one-year follow up*, <https://www.frontiersin.org/articles/10.3389/fgstr.2022.1063325/full>

**Public E2 Submission**

IPAY: 2026



| Question  | Sub-Question   | Response                                   |
|---|--|--|
| Question 26:<br>Respondent<br>Information                                 | Selected Drug  | VALSARTAN SACUBITRILAT                     |
|   | Q26 - Respondent Name  |  |
|   | Q26 - Organization Name<br>(if applicable)                                       | American Society for Preventive Cardiology |
|   | Respondent Email   |  |
| Question 27:<br>Prescribing<br>Information                                | Who is completing this<br>form?  | PAO  |
|   | Prescribing Information  | no response                                |
|   | Evidence Submitted include<br>a cost-effectiveness<br>measure?                   |  |
| Question 28:<br>Therapeutic<br>Impact and<br>Comparative<br>Effectiveness | What type of Evidence is<br>shown?   |  |
|   | Therapeutic Impact and<br>Comparative Effectiveness                              | no response                                |
|   | Hyperlink to<br>Table/Charts/Graphs -<br>Additional Materials for<br>Question 28 |  |
|   | Evidence Submitted include<br>a cost-effectiveness<br>measure?                   |  |
|   | What type of Evidence is<br>shown?   |  |
|   | Response to Question 29  | no response                                |

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| Question   | Sub-Question   | Response    |
|--|--|-------------|
| Question 29:<br>Comparative<br>Effectiveness<br>on Specific<br>Populations | Hyperlink to Citation -<br>Additional Materials for<br>Question 29               |             |
|  | Hyperlink to<br>Table/Charts/Graphs -<br>Additional Materials for<br>Question 29 |             |
|  | Evidence Submitted include<br>a cost-effectiveness<br>measure?                   |             |
|  | What type of Evidence is<br>shown?   |             |
| Question 30:<br>Addressing<br>Unmet<br>Medical<br>Needs                    | Response to Question 30  | no response |
|  | Hyperlink to Citation -<br>Additional Materials for<br>Question 30               |             |
|  | Hyperlink to<br>Table/Charts/Graphs -<br>Additional Materials for<br>Question 30 |             |
|  | Evidence Submitted include<br>a cost-effectiveness<br>measure?                   |             |
|  | What type of Evidence is<br>shown?   |             |

## Public E2 Submission

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| Question   | Sub-Question            | Response   |
|--|-------------------------|--|
| Question 31:<br>Patient and<br>Caregiver<br>Experience | Response to Question 31 |  |
| Question 32:<br>Executive<br>Summary                   | Response to Question 32 | <p>The American Society for Preventive Cardiology (ASPC), founded in 1985, represents the increasingly multidisciplinary group of healthcare providers, including nurses, nurse practitioners, dietitians, and other health specialists in addition to physicians, along with researchers who share in an interest in and passion for preventive cardiology. Our mission is to promote the prevention of cardiovascular disease, advocate for the preservation of cardiovascular health, and disseminate high-quality, evidence-based information through the education of healthcare clinicians and their patients...We appreciate the opportunity to provide comment on the Drug Price Negotiation Program that the Centers for Medicare and Medicaid Services (CMS) is pursuing for launch in 2026. Our society regularly advocates in partnership with other cardiovascular (CV) organizations to increase patient access to necessary therapy because, for cardiovascular and comorbid metabolic conditions, the need has never been greater. ..In fact, the death rate due to cardiovascular disease, after dropping more than 70% over a half century, has ticked up for some populations in America in recent decades.<sup>1</sup> Since 2011, according to CDC data, the death rate due to cardiovascular disease has only fallen by 4%.<sup>2</sup> It was once believed that cancer would overtake cardiovascular disease as the #1 killer of Americans. That seems no longer to be the case. ..It is estimated that nearly 7 million Americans are in heart failure, with nearly a million new cases yearly.<sup>3</sup> The common causes of heart failure include coronary artery disease, diabetes, obesity, and hypertension – which are all on the rise in America. Heart failure is a major challenge for the US. Innovative treatments like sacubitril-valsartan save and extend lives; indeed, sacubitril-valsartan is the first and only medicine to show significant mortality benefit compared to a widely used ACE inhibitor. Sacubitril-valsartan is not only associated with positive health benefits – it has also shown to save the health system money.<sup>4</sup>..The Inflation Reduction Act achieved several policy goals that we believe will make medications more affordable and will encourage patient adherence: namely, the patient out-of-pocket maximum and the smoothing mechanism that will ensure that cardiovascular patients are not hit with an unaffordable drug bill at the beginning of each plan year. Our society, as mentioned above, has also been involved with many initiatives to ensure that patient access and prescriber activity is not inhibited. We hope that through this process, CMS can ensure that patients can access these negotiated medications, like sacubitril-valsartan, without overburdening prescribers with utilization management policies designed to limit prescribing. ..Thank you. ...1. Betsy McKay for The Wall Street Journal. (2019, June 22). Heart attack at 49-America's biggest killer makes a deadly comeback. The Wall Street Journal. <a href="https://www.wsj.com/articles/after-decades-of-progress-america-backslides-on-heart-disease-11561129106">https://www.wsj.com/articles/after-decades-of-progress-america-backslides-on-heart-disease-11561129106</a> .2. State declines in heart disease mortality in the United States, 2000-2019. Accessed October 2, 2023. <a href="https://www.cdc.gov/nchs/data/databriefs/db425.pdf">https://www.cdc.gov/nchs/data/databriefs/db425.pdf</a> .3. Heart failure. Centers for Disease Control and Prevention. January 5, 2023. Accessed October 2, 2023.</p> |

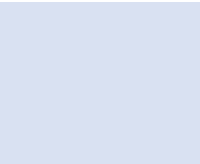


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| Question | Sub-Question |
|----------|--------------|
|----------|--------------|



|  |   |
|--|---|
|  | <p><b>Response</b></p> <p><a href="https://www.cdc.gov/heartdisease/heart_failure.htm">https://www.cdc.gov/heartdisease/heart_failure.htm</a>. .4. Gaziano TA, Fonarow GC, Velazquez EJ, Morrow DA, Braunwald E, Solomon SD. Cost-effectiveness of Sacubitril-Valsartan in hospitalized patients who have heart failure with reduced ejection fraction. JAMA cardiology. November 1, 2020. Accessed October 2, 2023. <a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7675099/">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7675099/</a>.</p> |
|--|---|



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| Question  | Sub-Question   | Response   |
|---|--|--|
| Question 26:<br>Respondent<br>Information                                 | Selected Drug  | VALSARTAN SACUBITRILAT   |
|   | Q26 - Respondent Name  |  |
|   | Q26 - Organization Name<br>(if applicable)                     | Chronic Care Policy Alliance   |
|   | Respondent Email<br>Who is completing this<br>form?            | PAO  |
| Question 27:<br>Prescribing<br>Information                                | Prescribing Information  | The Chronic Care Policy Alliance (CCPA) is a network of advocates focused on issues affecting patients living with chronic conditions. While we will let other disease-specific organizations offer their detailed perspectives on this drug, CCPA wishes to convey its views on how CMS should use the information gathered from the public. ..As CMS weighs information on how this product is prescribed and factors that information into the negotiation process, CMS should ensure that the negotiated price continues to support the patients using the product and their current usage. Patients using the product off-label or in different doses than the label should continue to have the same access after the negotiation process. Additionally, ensuring that the negotiation does not spur greater restrictions to access or utilization management, is also important to patients.  |
|   | Evidence Submitted include<br>a cost-effectiveness<br>measure? | N  |
|   | What type of Evidence is<br>shown?                             |  |
| Question 28:<br>Therapeutic<br>Impact and<br>Comparative<br>Effectiveness | Therapeutic Impact and<br>Comparative Effectiveness            | The Chronic Care Policy Alliance (CCPA) is a network of advocates focused on issues affecting patients living with chronic conditions. While we will let other disease-specific organizations offer their detailed perspectives on this drug, CCPA wishes to convey its views on how CMS should use the information gathered from the public...As CMS weighs information on the therapeutic impact and comparative effectiveness of this product, it is paramount that CMS recognize that individual patients may experience substantial benefit from a product that may not be apparent in aggregated data. Because of this, as CMS considers how this area factors into the overall price negotiation, CMS should ensure a negotiated price reflects the value the product provides to each unique patient. CCPA believes it is important that the incentives to continue developing treatments for chronic diseases be preserved, and it is important to reward the value treatments bring to patients. |

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| Question   | Sub-Question  | Response   |
|--|---|--|
|  | Hyperlink to Table/Charts/Graphs - Additional Materials for Question 28<br>Evidence Submitted include a cost-effectiveness measure?<br><br>What type of Evidence is shown?                                  |  |
|  | Response to Question 29   | The Chronic Care Policy Alliance (CCPA) is a network of advocates focused on issues affecting patients living with chronic conditions. While we will let other disease-specific organizations offer their detailed perspectives on this drug, CCPA wishes to convey its views on how CMS should use the information gathered from the public...Patients with chronic diseases all have their own unique experiences – in considering comparative effectiveness, CMS should weigh equally the experiences of individuals the same as measurements of experiences of specific populations – in a way that elevates all voices, instead of letting larger voices outweigh single patients. CCPA also encourages CMS to take into account populations that may be uniquely adversely affected by negotiation, such as specific patient populations that may face new utilization or formulary restrictions. In this way, CMS can ensure that it pursues a patient-centered approach. |
| Question 29: Comparative Effectiveness on Specific Populations | Hyperlink to Citation - Additional Materials for Question 29<br><br>Hyperlink to Table/Charts/Graphs - Additional Materials for Question 29<br><br>Evidence Submitted include a cost-effectiveness measure? |  |

## Public E2 Submission

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| Question  | Sub-Question   | Response   |
|---|--|--|
|   | What type of Evidence is shown?  |  |
| Question 30:<br>Addressing<br>Unmet<br>Medical<br>Needs | Response to Question 30  | The Chronic Care Policy Alliance (CCPA) is a network of advocates focused on issues affecting patients living with chronic conditions. While we will let other disease-specific organizations offer their detailed perspectives on this drug, CCPA wishes to convey its views on how CMS should use the information gathered from the public...CMS should ensure that its negotiation process on this product does not disadvantage any patient with an unmet medical need. Specifically, CMS should guard against the results of negotiations undercutting research into the product that may meet other unmet medical needs or may negatively impact the development of other products focused on unmet medical needs. |
|   | Hyperlink to Citation -<br>Additional Materials for<br>Question 30               |  |
|   | Hyperlink to<br>Table/Charts/Graphs -<br>Additional Materials for<br>Question 30 |  |
|   | Evidence Submitted include<br>a cost-effectiveness<br>measure?                   |  |
|   | What type of Evidence is shown?  |  |
| Question 31:<br>Patient and<br>Caregiver<br>Experience  | Response to Question 31  |  |
| Question 32:<br>Executive<br>Summary                    | Response to Question 32  |  |





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| Question  | Sub-Question   | Response               |
|---|--|------------------------|
| Question 26:<br>Respondent<br>Information                                 | Selected Drug  | VALSARTAN SACUBITRILAT |
|   | Q26 - Respondent Name  |                        |
|   | Q26 - Organization Name<br>(if applicable)                                       |                        |
|   | Respondent Email   |                        |
|   | Who is completing this<br>form?  | HCW                    |
| Question 27:<br>Prescribing<br>Information                                | Prescribing Information  |                        |
|   | Evidence Submitted include<br>a cost-effectiveness<br>measure?                   |                        |
|   | What type of Evidence is<br>shown?   |                        |
| Question 28:<br>Therapeutic<br>Impact and<br>Comparative<br>Effectiveness | Therapeutic Impact and<br>Comparative Effectiveness                              |                        |
|   | Hyperlink to<br>Table/Charts/Graphs -<br>Additional Materials for<br>Question 28 |                        |
|   | Evidence Submitted include<br>a cost-effectiveness<br>measure?                   |                        |
|   | What type of Evidence is<br>shown?   |                        |
|   | Response to Question 29  |                        |

## Public E2 Submission

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| Question   | Sub-Question   | Response |
|--|--|----------|
| Question 29:<br>Comparative<br>Effectiveness<br>on Specific<br>Populations | Hyperlink to Citation -<br>Additional Materials for<br>Question 29               |          |
|  | Hyperlink to<br>Table/Charts/Graphs -<br>Additional Materials for<br>Question 29 |          |
|  | Evidence Submitted include<br>a cost-effectiveness<br>measure?                   |          |
|  | What type of Evidence is<br>shown?   |          |
| Question 30:<br>Addressing<br>Unmet<br>Medical<br>Needs                    | Response to Question 30  |          |
|  | Hyperlink to Citation -<br>Additional Materials for<br>Question 30               |          |
|  | Hyperlink to<br>Table/Charts/Graphs -<br>Additional Materials for<br>Question 30 |          |
|  | Evidence Submitted include<br>a cost-effectiveness<br>measure?                   |          |
|  | What type of Evidence is<br>shown?   |          |

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| Question   | Sub-Question            | Response   |
|--|-------------------------|--|
| Question 31:<br>Patient and<br>Caregiver<br>Experience | Response to Question 31 |  |
| Question 32:<br>Executive<br>Summary                   | Response to Question 32 | <p>Thank you for the opportunity to provide comments on Entresto for the Medicare Drug Price Negotiation Program for initial price applicability year 2026. ..I am a cardiologist based in Memphis, TN and serve patients in both Tennessee and Mississippi. I am a fellow of the National Lipid Association, the American Society for Preventive Cardiology, the American College of Cardiology and serve on a number of boards supporting cardiovascular patients and providers. ..The state of Mississippi, where most of my patients call home, has the worst rates of cardiovascular disease and cardiovascular death in the country. My colleagues and I oftentimes feel that we are on the front lines battling the #1 killer not only in our state, but in the country as well. Recent data published in JAMA Cardiology found that the residents of Mississippi are in fact 50% more likely to die of heart failure than people who live in any other state. Mississippi's rates of death to cardiovascular disease in fact septuple those of other states.<sup>1</sup> ..Having therapies available to treat my patients is of the utmost importance, and Entresto provides immense value for my patients. ..Sacubitril-valsartan is the first and only angiotensin receptor-neprilysin inhibitor approved for heart failure by the FDA and is an American Heart Association/American College of Cardiology/Heart Failure Society of America guideline-recommended treatment for individuals with reduced ejection fraction (HFrEF). Real world data has shown that sacubitril-valsartan, compared with enalapril, prevented over 50,000 hospitalizations in the United States and saves our health system tens of millions of dollars.<sup>2</sup> ..I am grateful that the legislation that promulgated the Medicare Drug Price Negotiation Program capped out-of-pocket maximums for drugs and created a mechanism that America's seniors can pay down their deductible over the course of a plan year. However, I must impress upon you that any cost savings that are negotiated through this program must be passed to the patient. Individuals that I treat who are on agents like sacubitril-valsartan often have comorbidities and are taking many medications to treat their cardiovascular disease and/or metabolic conditions. If cost savings from this program are not passed to the patient, then patient-centered care is transparently not the goal of the program. Furthermore, if access to these medications is limited as a result of this program, the results could be disastrous for patient health and outcomes. Please ensure that access remains open. ..Thank you. ...1. Jain, V., Minhas, A. M. K., Morris, A. A., Greene, S. J., Pandey, A., Khan, S. S., Fonarow, G. C., Mentz, R. J., Butler, J., &amp; Khan, M. S. (2022). Demographic and regional trends of Heart Failure–Related mortality in young adults in the US, 1999-2019. JAMA Cardiology, 7(9), 900. <a href="https://doi.org/10.1001/jamacardio.2022.2213">https://doi.org/10.1001/jamacardio.2022.2213</a> ..2. Gaziano TA, Fonarow GC, Velazquez EJ, Morrow DA, Braunwald E, Solomon SD. Cost-effectiveness of Sacubitril-Valsartan in Hospitalized Patients Who Have Heart Failure With Reduced Ejection Fraction. JAMA Cardiol. 2020 Nov 1;5(11):1236-1244. doi: 10.1001/jamacardio.2020.2822. PMID: 32785628; PMCID: PMC7675099.</p> |



**Public E2 Submission**

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| Question  | Sub-Question   | Response               |
|---|--|------------------------|
| Question 26:<br>Respondent<br>Information                                 | Selected Drug  | VALSARTAN SACUBITRILAT |
|   | Q26 - Respondent Name  |                        |
|   | Q26 - Organization Name<br>(if applicable)                                       |                        |
|   | Respondent Email   |                        |
|   | Who is completing this<br>form?  | HCW                    |
| Question 27:<br>Prescribing<br>Information                                | Prescribing Information  | None                   |
|   | Evidence Submitted include<br>a cost-effectiveness<br>measure?                   |                        |
|   | What type of Evidence is<br>shown?   |                        |
| Question 28:<br>Therapeutic<br>Impact and<br>Comparative<br>Effectiveness | Therapeutic Impact and<br>Comparative Effectiveness                              | None                   |
|   | Hyperlink to<br>Table/Charts/Graphs -<br>Additional Materials for<br>Question 28 |                        |
|   | Evidence Submitted include<br>a cost-effectiveness<br>measure?                   |                        |
|   | What type of Evidence is<br>shown?   |                        |
|   | Response to Question 29  | None                   |

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| Question   | Sub-Question   | Response |
|--|--|----------|
| Question 29:<br>Comparative<br>Effectiveness<br>on Specific<br>Populations | Hyperlink to Citation -<br>Additional Materials for<br>Question 29               |          |
|  | Hyperlink to<br>Table/Charts/Graphs -<br>Additional Materials for<br>Question 29 |          |
|  | Evidence Submitted include<br>a cost-effectiveness<br>measure?                   |          |
|  | What type of Evidence is<br>shown?   |          |
| Question 30:<br>Addressing<br>Unmet<br>Medical<br>Needs                    | Response to Question 30  | None     |
|  | Hyperlink to Citation -<br>Additional Materials for<br>Question 30               |          |
|  | Hyperlink to<br>Table/Charts/Graphs -<br>Additional Materials for<br>Question 30 |          |
|  | Evidence Submitted include<br>a cost-effectiveness<br>measure?                   |          |
|  | What type of Evidence is<br>shown?   |          |



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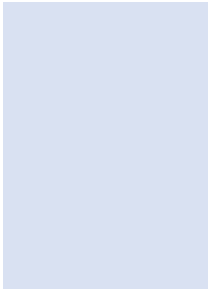
| Question   | Sub-Question            | Response  |
|--|-------------------------|---|
| Question 31:<br>Patient and<br>Caregiver<br>Experience | Response to Question 31 |   |
| Question 32:<br>Executive<br>Summary                   | Response to Question 32 | <p>Thank you for the opportunity to provide comments on sacubitril-valsartan for the Medicare Drug Price Negotiation Program for initial price applicability in year 2026. .I am a cardiologist by training, a researcher and clinical affiliate professor of cardiology at FAU Medical School. I am the past president of the American Society for Preventive Cardiology, a fellow of the American College of Cardiology, the American Heart Association, the American College of Preventive Medicine, the National Lipid Association, and a Master of the American Society for Preventive Cardiology. I have devoted my life to cardiology and the transformative power of preventive medicine. .As you know, heart failure is remarkably common in America. Although in recent years we have made impressive gains in understanding and treating many forms of cardiovascular disease, heart failure remains a growing problem. The Heart Failure Society of America estimates that nearly 6.5 million Americans have heart failure, with nearly 1 million new cases annually.<sup>1</sup> This burden, understandably, rests heaviest on the Medicare population, and heart failure is now indicated on more than 13.4% of death certificates.<sup>2</sup> .These statistics alone illuminate the value of a medication like sacubitril-valsartan, which is the only angiotensin receptor-neprilysin inhibitor (ARNi) approved by FDA to treat heart failure. Not only is this medication effective, but studies show that it saves the healthcare system money. An important study looking at the cost effectiveness of sacubitril-valsartan showed that inpatient treatment was cost saving to the healthcare system. The study also showed an increase in quality-adjusted life expectancy and an association with fewer hospitalizations.<sup>3</sup> Cardiologists wait our entire careers for medications like this that can help both patients and society at large. .The Medicare Drug Price Negotiation Program's stated aim is to lower the price of drugs for Medicare beneficiaries. I am deeply concerned, however, that patients will not actually realize lower prices at the pharmacy counter, as there has been no stated guarantee that cost savings from negotiation will be passed to patients. I am also deeply concerned that without checks, balances, and assurances from pharmacy benefit managers administering formularies, patients will face higher utilization management barriers such as prior authorization, nonmedical switching, and step therapy protocols for negotiated drugs like sacubitril-valsartan. Such practices will likely cause great harm to patients.<sup>3</sup> CMS needs to ensure that negotiation accurately reflects the immense value medications like sacubitril-valsartan offer to the Medicare program and to patients themselves; CMS must also ensure that through implementation of the program, access to needed therapy is not limited.</p> <p>1. Heart Failure Facts &amp; Information. (n.d.). Heart Failure Society of America. <a href="https://hfsa.org/patient-hub/heart-failure-facts-information#:~:text=Current%20estimates%20are%20that%20nearly,new%20heart%20failure%20cases%20annually">https://hfsa.org/patient-hub/heart-failure-facts-information#:~:text=Current%20estimates%20are%20that%20nearly,new%20heart%20failure%20cases%20annually</a></p> <p>2. Virani, S. S., Alonso, Á., Benjamin, E. J., Bittencourt, M. S., Callaway, C. W., Carson, A. P., Chamberlain, A. M., Chang, A. R., Cheng, S., Delling, F. N., Djoussé, L., Elkind, M. S., Ferguson, J. F., Fornage, M., Khan, S. S., Kissela, B. M.,</p> |

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Question      Sub-Question



Response

Knutson, K. L., Kwan, T., Lackland, D. T., . . . Tsao, C. W. (2020). Heart disease and stroke statistics – 2020 Update: A report from the American Heart Association. *Circulation*, 141(9). <https://doi.org/10.1161/cir.0000000000000757>

3.      Gaziano TA, Fonarow GC, Velazquez EJ, Morrow DA, Braunwald E, Solomon SD. Cost-effectiveness of Sacubitril-Valsartan in Hospitalized Patients Who Have Heart Failure With Reduced Ejection Fraction. *JAMA Cardiol.* 2020 Nov 1;5(11):1236-1244. doi: 10.1001/jamacardio.2020.2822. PMID: 32785628; PMCID: PMC7675099.

4.      The Impact of Non-Medical Switching on Patients Taking a Blood Thinner. (2022, August). American Society for Preventive Cardiology. <https://www.aspconline.org/wp-content/uploads/2022/08/ASPC-NMSBloodThinner-SurveyReport-August2022.pdf>



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| Question  | Sub-Question   | Response  |
|---|--|---|
| Question 26:<br>Respondent<br>Information                                 | Selected Drug  | VALSARTAN SACUBITRILAT  |
|   | Q26 - Respondent Name  |   |
|   | Q26 - Organization Name<br>(if applicable)                                       |   |
|   | Respondent Email   |   |
|   | Who is completing this<br>form?  | HCW   |
| Question 27:<br>Prescribing<br>Information                                | Prescribing Information  | I have been a hospital pharmacist for almost 40 years. The number of patients who are admitted to the hospital because they cannot afford their prescription medicines continues to grow. Americans pay some of the highest drug prices in the world due to the corporate greed of the drug companies. The companies lie about the cost to bring a new drug to market and waste millions of dollars on unscrupulous advertisements. Entresto is part of GDMT, and as such, should be affordable to the average American. Price negotiations are LONG overdue. I wholeheartedly support this endeavor. |
|   | Evidence Submitted include<br>a cost-effectiveness<br>measure?                   |   |
|   | What type of Evidence is<br>shown?   |   |
| Question 28:<br>Therapeutic<br>Impact and<br>Comparative<br>Effectiveness | Therapeutic Impact and<br>Comparative Effectiveness                              |   |
|   | Hyperlink to<br>Table/Charts/Graphs -<br>Additional Materials for<br>Question 28 |   |
|   | Evidence Submitted include<br>a cost-effectiveness<br>measure?                   |   |

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| Question  | Sub-Question  | Response |
|---|---|----------|
|   | What type of Evidence is shown?   |          |
| Question 29:<br>Comparative Effectiveness on Specific Populations | Response to Question 29   |          |
|   | Hyperlink to Citation - Additional Materials for Question 29  |          |
|   | Hyperlink to Table/Charts/Graphs - Additional Materials for Question 29   |          |
|   | Evidence Submitted include a cost-effectiveness measure?  |          |
|   | What type of Evidence is shown?   |          |
| Question 30:<br>Addressing Unmet Medical Needs                    | Response to Question 30   |          |
|   | Hyperlink to Citation - Additional Materials for Question 30<br>Hyperlink to Table/Charts/Graphs - Additional Materials for Question 30 |          |

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| Question                                      | Sub-Question   | Response |
|---|--|----------|
|   | Evidence Submitted include a cost-effectiveness measure? |          |
|   | What type of Evidence is shown?                          |          |
| Question 31: Patient and Caregiver Experience | Response to Question 31                                  |          |
| Question 32: Executive Summary                | Response to Question 32                                  |          |





**Public E2 Submission**

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| Question  | Sub-Question   | Response               |
|---|--|------------------------|
| Question 26:<br>Respondent<br>Information                                 | Selected Drug  | VALSARTAN SACUBITRILAT |
|   | Q26 - Respondent Name  |                        |
|   | Q26 - Organization Name<br>(if applicable)                                       |                        |
|   | Respondent Email   |                        |
|   | Who is completing this<br>form?  | HCW                    |
| Question 27:<br>Prescribing<br>Information                                | Prescribing Information  |                        |
|   | Evidence Submitted include<br>a cost-effectiveness<br>measure?                   |                        |
|   | What type of Evidence is<br>shown?   |                        |
| Question 28:<br>Therapeutic<br>Impact and<br>Comparative<br>Effectiveness | Therapeutic Impact and<br>Comparative Effectiveness                              |                        |
|   | Hyperlink to<br>Table/Charts/Graphs -<br>Additional Materials for<br>Question 28 |                        |
|   | Evidence Submitted include<br>a cost-effectiveness<br>measure?                   |                        |
|   | What type of Evidence is<br>shown?   |                        |
|   | Response to Question 29  |                        |

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| Question  | Sub-Question  | Response   |
|---|---|--|
| Question 29:<br>Comparative Effectiveness on Specific Populations | Hyperlink to Citation - Additional Materials for Question 29                                    |  |
|   | Hyperlink to Table/Charts/Graphs - Additional Materials for Question 29                         |  |
|   | Evidence Submitted include a cost-effectiveness measure?<br><br>What type of Evidence is shown? |  |
| Question 30:<br>Addressing Unmet Medical Needs                    | Response to Question 30   | Patient Story. Patient JC is an advanced failure patient previously requiring inotrope drip. Post discharge, outpatient providers are working to get him on appropriate GDMT. However, he is unable to start Entresto due to high out of pocket cost of \$600 for a month's supply. Heart Failure nurses are helping the patient apply for patient assistance through the drug manufacturer, but this has been taking about a month for patient to complete. They patient is unable to obtain the full recommended medications for his heart failure until there is a decision on his patient assistance program approval. |
|   | Hyperlink to Citation - Additional Materials for Question 30                                    |  |
|   | Hyperlink to Table/Charts/Graphs - Additional Materials for Question 30                         |  |
|   | Evidence Submitted include a cost-effectiveness measure?  |  |

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| Question   | Sub-Question                    | Response  |
|--|---------------------------------|---|
|  | What type of Evidence is shown? |   |
| Question 31:<br>Patient and<br>Caregiver<br>Experience | Response to Question 31         |   |
| Question 32:<br>Executive<br>Summary                   | Response to Question 32         | <p>I am a nurse practitioner with the Heart Failure Clinic at [REDACTED]. Every day I work to start patients on guideline directed medical therapy according to the 2022 American Heart Association and American College of Cardiology guidelines as I know these medications are proven through research to improve my patients' outcomes with reduced risk of death and heart failure hospitalization. I have also personally seen the benefits of these medications. I have had patients come back and tell me after starting Entresto that they felt better. They could breathe easier and do more activities around their house. I have prescribed Farxiga and Jardiance and had patients come back and tell me their abdomens feel less bloated and their breathing is easier. I have also seen the power of these medications at work on the left ventricle. When I was able to get a patient on all four heart failure medications, I have seen the echocardiogram show recovery of the heart muscle. I believe in the heart failure medications. The biggest hurdle though is not prescribing guideline-directed medical therapy, it is getting patients able to afford the medications to take them. At my office we try manufacturer coupons for those with commercial insurance and patients with Medicare we always try patient assistance programs through the manufacturers. Patients are so excited when they qualify for these programs and can continue their medications. Unfortunately, we have had patients who do not qualify and have had to stop taking their heart failure medications and use alternatives such as ACE-I or ARB which do not have the benefit of Entresto. Also, there is no therapeutic alternative for SGLT2 such as Jardiance and Farxiga, so those patients just have to go without one medication in the pillars of heart failure guideline-medical therapy. As an advocate for my patients, please negotiate the lowering of these essential heart failure medications so that all my patients can afford to take these lifesaving medications. The current costs of these drugs have created a health inequity where only patients with commercial insurance or the wealthy can take the necessary heart failure medications, whereas the underserved population on Medicare has to go without. Please join me in standing up for these patients and ensuring all Americans with heart failure have equal access to treatment. Thank you...Response from Coworker.As a nurse practitioner working in the heart failure field for the past ten years, I have had innumerable Medicare patients who have not been able to access the best medical therapy for their condition due to inadequate drug coverage by Medicare. This results in suboptimal treatment of this high-risk, vulnerable population. ..The drugs that are most commonly cost-prohibitive for my Medicare patients include: entresto, farxiga, jardiance, xarelto and eliquis. I expect to see anywhere from one to ten patients per week who are unable to afford one of these medications. In most of these cases, we wind</p> |



Question      Sub-Question

**Response**  
up having to pursue patient assistance programs to try to get these drugs covered. Even if they wind up being accepted to the patient assistance programs, this is time-consuming for our nursing staff and results in delays in treatment. While waiting for the preferred treatment to arrive, we often have patients on cheaper and less favorable options (for example, we may use valsartan or losartan in place of entresto until the entresto is approved and available). Once the patient receives the medication via a patient assistance program, they are then required to transition from one therapy to another. This results in many medication errors - patients often wind up continuing therapy and then are on duplicate medications...Patients who are unable to access NOACs (xarelto, eliquis), wind up having to be on the cheaper alternative: warfarin. Warfarin is thought of as inferior to xarelto and eliquis and has more risks associated with it. It requires titration of the dose to achieve a therapeutic level of the drug. This puts a burden on the patient to both get frequent labs and then adjust the medication dosing. This can be a challenging task for elderly patients and unfortunately can result in medication errors...There is great evidence behind the use of entresto and SGLT2i inhibitors in heart failure: these medications have been shown to reduce re-hospitalization and improve survival; I hope that Medicare prioritizes making these medications accessible to a larger volume of patients. Perhaps it would help reduce the amount they are paying for rehospitalization of heart failure patients....Thank you.. [REDACTED]





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| Question  | Sub-Question                                     | Response                |
|---|--|-------------------------|
| Question 26: Respondent Information                           | Selected Drug                                    | VALSARTAN SACUBITRILAT  |
|   | Q26 - Respondent Name                            |                         |
|   | Q26 - Organization Name (if applicable)          | The Mended Hearts, Inc. |
|   | Respondent Email                                 |                         |
|   | Who is completing this form?                     | PAO                     |
| Question 27: Prescribing Information                          | Prescribing Information                          | No response.            |
|   | Evidence Submitted                               |                         |
|   | include a cost-effectiveness measure?            |                         |
| Question 28: Therapeutic Impact and Comparative Effectiveness | What type of Evidence is shown?                  |                         |
|   | Therapeutic Impact and Comparative Effectiveness | No response.            |
|   | Hyperlink to Table/Charts/Graphs -               |                         |
|   | Additional Materials for Question 28             |                         |

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| Question   | Sub-Question  | Response     |
|--|---|--------------|
|  | Evidence Submitted include a cost-effectiveness measure?                |              |
|  | What type of Evidence is shown?   |              |
| Question 29: Comparative Effectiveness on Specific Populations | Response to Question 29   | No response. |
|  | Hyperlink to Citation - Additional Materials for Question 29            |              |
|  | Hyperlink to Table/Charts/Graphs - Additional Materials for Question 29 |              |
|  | Evidence Submitted include a cost-effectiveness measure?                |              |
|  | What type of Evidence is shown?   |              |
| Question 30:   | Response to Question 30   | No response. |

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| Question                                      | Sub-Question  | Response   |
|---|---|--|
| Addressing Unmet Medical Needs                | <p>Hyperlink to Citation - Additional Materials for Question 30</p> <p>Hyperlink to Table/Charts/Graphs - Additional Materials for Question 30</p> <p>Evidence Submitted include a cost-effectiveness measure?</p> <p>What type of Evidence is shown?</p> |  |
| Question 31: Patient and Caregiver Experience | Response to Question 31   |  |
| Question 32: Executive Summary                | Response to Question 32   | <p>Mended Hearts is the largest cardiovascular peer-to-peer patient support group in the country. We provide support and education, bring awareness to issues that those living with heart disease face and advocate to improve quality of life. Since our inception in 1951, we have assisted millions in their journey with heart disease. ..Our support network helps individuals with various cardiovascular conditions. Most often, patients find Mended Hearts because they have suffered a traumatic cardiovascular event, and they need a peer to help them navigate the physical, mental and emotional challenges of cardiovascular disease and its unfortunate consequences. ..We would like to focus our comments on a disease that impacts many of our members, which is heart failure. By 2030, heart failure (HF) is anticipated to affect more than 8 million individuals, representing a 46% increase from 2012.<sup>1</sup> Sacubitril-valsartan is the only angiotensin receptor-neprilysin inhibitor (ARNi) approved by the FDA for the treatment of heart failure in the United States. A recent</p> |

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Question

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Sub-Question

Response

HHS fact sheet showed that beneficiaries only pay approximately \$29 per month on average for sacubitril-valsartan. Sacubitril-valsartan also has demonstrated that it reduces hospitalizations, emergency visits, and premature death for over 500,000 Medicare beneficiaries.<sup>2</sup> Mended Hearts serves thousands of our nation's seniors, and we were relieved to see that the Inflation Reduction Act capped out-of-pocket spending for Medicare beneficiaries and smoothed out deductibles so seniors can pay their bills over the course of the year. Our members, however, do face numerous access challenges. Many cardiovascular patients suffer from a number of comorbid conditions and are therefore managing conditions with multiple medications. Prior authorization hurdles, non-medical switching and step therapy protocols can make "being a patient" a full-time job. We hope that CMS negotiations will ensure that patients like our members are protected from burdensome utilization management, and that they actually see the benefit of these new prices at the pharmacy counter. We believe that including the patient voice in policy conversations is of the utmost importance, and we work to ensure that our patient advocates have opportunities to interface with their elected representatives and those that administer agencies like the Centers for Medicare and Medicaid Services (CMS). We are grateful that CMS has provided an opportunity to comment on the Drug Price Negotiation Program. <sup>1</sup> Heart failure projected to increase dramatically, according to New Statistics. [www.heart.org](https://www.heart.org/en/news/2018/05/01/heart-failure-projected-to-increase-dramatically-according-to-new-statistics). August 16, 2021. Accessed October 2, 2023. <sup>2</sup> Pascual-Figal D, Bayés-Genis A, Beltrán-Troncoso P, et al. Sacubitril-Valsartan, clinical benefits and related mechanisms of action in heart failure with reduced ejection fraction. A Review. *Frontiers*. October 6, 2021. Accessed October 2, 2023. <https://www.frontiersin.org/articles/10.3389/fcvm.2021.754499/full#:~:text=Sacubitril%2Fvalsartan%20is%20the%20first%20of%20the%20class%20of,and%20rehospitalization%20for%20HF%20when%20compared%20to%20enalapril>.



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| Question  | Sub-Question   | Response  |
|---|--|---|
| Question 26:<br>Respondent<br>Information                                 | Selected Drug  | VALSARTAN SACUBITRILAT                              |
|   | Q26 - Respondent Name  |   |
|   | Q26 - Organization Name<br>(if applicable)                                       | Partnership to Advance Cardiovascular Health (PACH) |
|   | Respondent Email   |   |
| Question 27:<br>Prescribing<br>Information                                | Who is completing this<br>form?  | PAO   |
|   | Prescribing Information  |   |
|   | Evidence Submitted include<br>a cost-effectiveness<br>measure?                   |   |
| Question 28:<br>Therapeutic<br>Impact and<br>Comparative<br>Effectiveness | What type of Evidence is<br>shown?   |   |
|   | Therapeutic Impact and<br>Comparative Effectiveness                              |   |
|   | Hyperlink to<br>Table/Charts/Graphs -<br>Additional Materials for<br>Question 28 |   |
|   | Evidence Submitted include<br>a cost-effectiveness<br>measure?                   |   |
|   | What type of Evidence is<br>shown?   |   |
|   | Response to Question 29  |   |



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| Question   | Sub-Question   | Response |
|--|--|----------|
| Question 29:<br>Comparative<br>Effectiveness<br>on Specific<br>Populations | Hyperlink to Citation -<br>Additional Materials for<br>Question 29               |          |
|  | Hyperlink to<br>Table/Charts/Graphs -<br>Additional Materials for<br>Question 29 |          |
|  | Evidence Submitted include<br>a cost-effectiveness<br>measure?                   |          |
|  | What type of Evidence is<br>shown?   |          |
| Question 30:<br>Addressing<br>Unmet<br>Medical<br>Needs                    | Response to Question 30  |          |
|  | Hyperlink to Citation -<br>Additional Materials for<br>Question 30               |          |
|  | Hyperlink to<br>Table/Charts/Graphs -<br>Additional Materials for<br>Question 30 |          |
|  | Evidence Submitted include<br>a cost-effectiveness<br>measure?                   |          |
|  | What type of Evidence is<br>shown?   |          |

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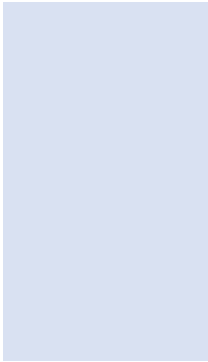
| Question   | Sub-Question            | Response   |
|--|-------------------------|--|
| Question 31:<br>Patient and<br>Caregiver<br>Experience | Response to Question 31 |  |
| Question 32:<br>Executive<br>Summary                   | Response to Question 32 | <p>The Partnership to Advance Cardiovascular Health (PACH) is a nonprofit advocacy coalition of stakeholder groups that represent cardiovascular patients, patient advocates, health care providers, and medical researchers. On behalf of its members, PACH advocates for patient access to FDA-approved therapies and promotes innovation in cardiovascular healthcare for the millions of Americans at high risk for heart disease. ..Cardiovascular medicine has benefited from many years of breakthrough research, which has led to highly effective treatments that have enabled seniors to live longer, healthier lives. However, heart disease continues to be the #1 killer in America, accounting for 1 in every 5 deaths in 2021. ..Cardiovascular disease disproportionately impacts vulnerable communities, including minorities, aging populations, rural communities, and those with lower socioeconomic status. For example, black men have a 70% higher risk of heart failure (HF), and black women have a 50% higher risk than their white counterparts. Yet racial and ethnic minorities receive less than 40% of total annual advanced HF therapies – and women receive less than a quarter. Similarly, atrial fibrillation (AF) is the most common cardiac arrhythmia in the United States, and patients with AF are five times more likely to experience an ischemic stroke. Medicare claims studies have shown that Black and Hispanic patients over 65 with AF had a higher unadjusted risk of death and stroke. ..Sacubitril-valsartan is the first and only angiotensin receptor-neprilysin inhibitor approved for heart failure by the FDA and is a guideline-recommended treatment for individuals with reduced ejection fraction (HFrEF). Sacubitril, a neprilysin inhibitor, controls blood volume, and valsartan, an angiotensin II receptor, prevents tightening of the blood vessels which helps the heart function more efficiently.<sup>1</sup> This combination ultimately lowers the risk of death and hospitalization in adults with chronic heart failure. Real world data has shown that sacubitril-valsartan, compared with ACE inhibitors, prevents hospitalizations and saves our healthcare system tens of millions of dollars.<sup>2</sup> ..As organizations that represent cardiovascular patients and prescribers, we believe it is notable that cardiovascular agents are disproportionately represented in price negotiations. Our goal is to ensure that the 42% of Medicare beneficiaries who have been diagnosed with a heart condition can still receive current and future medications they need to prevent heart attacks and strokes. While we steadfastly agree that lowering the cost of medications for our vulnerable seniors is a priority, we remain concerned that the Inflation Reduction Act Medicare Drug Price Negotiation Program could negatively impact innovation and access to life-saving medications. ..If patients are nonmedically switched off sacubitril/valsartan, then we can expect an uptick in hospitalizations and deaths, which will result in higher costs for patients, insurances companies, PBMs, and the government. If CMS ensures access to medicines like sacubitril/valsartan is not limited by negotiations, then we can avoid this outcome, but CMS must keep the patient at the center of these negotiations to avoid this. ..We recognize IRA has implications for future</p> |

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Question      Sub-Question



Response

research and development as well as access to current medicines. We urge CMS to take steps now to ensure the drug negotiation program is patient-centric and equitable for the millions of Medicare beneficiaries diagnosed with cardiovascular disease today and in the long run. If PACH or our members can be a resource to CMS, please do not hesitate to contact us. Considering that the IRA will disproportionately impact cardiovascular patients, we would welcome meeting with CMS to discuss our concerns and offer insights from the community. ..1. Valsartan and Sacubitril: Medlineplus Drug Information. MedlinePlus. Accessed October 2, 2023. <https://medlineplus.gov/druginfo/meds/a615039.html>. ..2. Gaziano TA, Fonarow GC, Velazquez EJ, Morrow DA, Braunwald E, Solomon SD. Cost-effectiveness of Sacubitril-Valsartan in Hospitalized Patients Who Have Heart Failure With Reduced Ejection Fraction. JAMA Cardiol. 2020 Nov 1;5(11):1236-1244. doi: 10.1001/jamacardio.2020.2822. PMID: 32785628; PMCID: PMC7675099.



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| Question  | Sub-Question   | Response                            |
|---|--|-------------------------------------|
| Question 26:<br>Respondent<br>Information                                 | Selected Drug  | VALSARTAN SACUBITRILAT              |
|   | Q26 - Respondent Name  |                                     |
|   | Q26 - Organization Name<br>(if applicable)                                       | Patients for Affordable Drugs, P4AD |
|   | Respondent Email   |                                     |
| Question 27:<br>Prescribing<br>Information                                | Who is completing this<br>form?  | PAO                                 |
|   | Prescribing Information  |                                     |
|   | Evidence Submitted include<br>a cost-effectiveness<br>measure?                   |                                     |
|   | What type of Evidence is<br>shown?   |                                     |
| Question 28:<br>Therapeutic<br>Impact and<br>Comparative<br>Effectiveness | Therapeutic Impact and<br>Comparative Effectiveness                              |                                     |
|   | Hyperlink to<br>Table/Charts/Graphs -<br>Additional Materials for<br>Question 28 |                                     |
|   | Evidence Submitted include<br>a cost-effectiveness<br>measure?                   |                                     |
|   | What type of Evidence is<br>shown?   | Y                                   |
|   | Response to Question 29  |                                     |

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| Question   | Sub-Question   | Response |
|--|--|----------|
| Question 29:<br>Comparative<br>Effectiveness<br>on Specific<br>Populations | Hyperlink to Citation -<br>Additional Materials for<br>Question 29               |          |
|  | Hyperlink to<br>Table/Charts/Graphs -<br>Additional Materials for<br>Question 29 |          |
|  | Evidence Submitted include<br>a cost-effectiveness<br>measure?                   |          |
|  | What type of Evidence is<br>shown?   |          |
| Question 30:<br>Addressing<br>Unmet<br>Medical<br>Needs                    | Response to Question 30  |          |
|  | Hyperlink to Citation -<br>Additional Materials for<br>Question 30               |          |
|  | Hyperlink to<br>Table/Charts/Graphs -<br>Additional Materials for<br>Question 30 |          |
|  | Evidence Submitted include<br>a cost-effectiveness<br>measure?                   |          |
|  | What type of Evidence is<br>shown?   |          |



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| Question   | Sub-Question            | Response |
|--|-------------------------|----------|
| Question 31:<br>Patient and<br>Caregiver<br>Experience | Response to Question 31 |          |
| Question 32:<br>Executive<br>Summary                   | Response to Question 32 |          |



Unfortunately, as a Type 1 Diabetic for over 51 years, I had an emergency triple bypass procedure back in 2020. As I went through Cardiac Rehab my Cardiologist prescribed Entresto 24-26 2x's times a day. This is a new drug and there are no other substitutes. He stated it was a new revolutionary drug for Heart Failure which is my diagnosis.

As I struggle, with other drug costs ( diabetes) Entresto's list price today is \$667.97. I receive 90 day supply which is a Tier 3 drug under Medicare Part D which has deductibles and the donut hole that really can add on to your out of pocket costs. This has been an extraordinary expense for me. This year so far I have paid \$529.04 and \$565.00 = \$1094.00 based on Part D deductibles and donut hole. I will still need another script by years end. I have been told Entresto is essential for those that have heart failure. HAHA when I saw the price I thought I was going to have another heart issue!! It certainly has kept my heart at the proper ejection fraction.

This along with dealing with this cardiac issue, other drugs/supplies for diabetes has really worried me about my families financial future. The IRA and Medicare negotiations of drug prices is an historic move that will save patients and Government enormous amounts of money. Estimates over time are in the billions. As I see it, this is so needed at this time. We will finally be cracking down on price gouging, capping out of pocket costs \$2000 for Medicare Patients like me. This is very key to out of pocket costs for all.

The Medicare negotiations will help me and so many others— control our costs, have fair, predicable and equitable pricing especially for chronic illness. We will be able to predict our costs more efficiently, not worry so much about our nest eggs we have worked for all our lives. I'd be able to see my Grandkids more often, travel and afford

things that I cannot purchase today because of my fear of my drug costs. Others it could mean life or death!!

For Medicare these top 10 selected drugs, Entresto included, accounted for \$50.5 Billion in total Part D gross covered drugs. Medicare drug price negotiations could save government billions!!! Don't we want to cut back on spending and watch the budget more closely? US adults believe the cost of prescription drugs are unreasonable, with roughly 1 and 3 reporting that they cannot afford to take their medications as prescribed. Rationing!! We all do it.

What if I stop taking Entresto/Insulin that would be a very bad situation for me. Death is possible. This fact is a very sad state of affairs for patients taking Entresto and other drug for a long term illness. CMS, thank you so much for listening to everyday patients to hear their struggles and make some much needed changes.

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| Question  | Sub-Question   | Response  |
|---|--|---|
| Question 26:<br>Respondent<br>Information                                 | Selected Drug  | VALSARTAN SACUBITRILAT  |
|   | Q26 - Respondent Name  |   |
|   | Q26 - Organization Name<br>(if applicable)   | Pharmaceutical Care Management Association (PCMA)   |
|   | Respondent Email<br>Who is completing this<br>form?  | TRD   |
| Question 27:<br>Prescribing<br>Information                                | Prescribing Information  |   |
|   | Evidence Submitted include<br>a cost-effectiveness<br>measure?<br>What type of Evidence is<br>shown? |   |
| Question 28:<br>Therapeutic<br>Impact and<br>Comparative<br>Effectiveness | Therapeutic Impact and<br>Comparative Effectiveness  | <p>The Pharmaceutical Care Management Association (PCMA) appreciates the opportunity to submit comments regarding the therapeutic alternatives for Valsartan/Sacubitrilat. Our members help administer the Part D prescription drug benefit on behalf of many Part D plan sponsors, and a central component of that function is the identification of therapeutic alternatives to develop comprehensive prescription drug formularies consistent with applicable statutory, regulatory, and clinical requirements, including ensuring formularies are not discriminatory...In general, while we understand that CMS cannot disclose the specifics of their negotiations with manufacturers of selected drugs, we believe the public is best served by CMS disclosing as much about this process as possible, and otherwise aligning its methodology for selecting therapeutic alternatives with how Part D plans select therapeutic alternatives. Our comments focus on emphasizing the differences between identifying therapeutic alternatives for purposes of the Medicare Drug Price Negotiation Program, and the role that the identification of therapeutic alternatives plays under the Medicare Part D program's formulary standards and enrollee communication requirements. PCMA has three main points:...</p> <p>1. As a general principle, CMS should identify therapeutic alternatives under the Medicare Drug Price Negotiation Program consistent with the guardrails that apply to Part D plan sponsors when identifying therapeutic alternatives for the Part D program. ...2. CMS should clarify in an HPMS memo to Part D plans that CMS's identification of therapeutic alternatives for the Medicare Drug Price Negotiation Program will not impact the agency's existing approach towards evaluating Part D formulary design for compliance with Part D</p> |

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| Question | Sub-Question | Response |
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|  |  | <p>formulary requirements...3. CMS should clarify in an HPMS memo that Part D plans retain discretion on how to communicate therapeutic alternatives to enrollees, and that CMS's identification of therapeutic alternatives for purposes of the Medicare Drug Price Negotiation Program will not affect these enrollee communications...We discuss these issues in more detail below...I. CMS should identify therapeutic alternatives under the Medicare Drug Price Negotiation Program consistent with the guardrails that apply to Part D plan sponsors when identifying therapeutic alternatives for their formulary submissions. ..Currently, Part D plan sponsors consider a variety of factors when identifying therapeutic alternatives for their formulary submissions, including but not limited to (i) clinical effectiveness, (ii) safety, (iii) price, (iv) availability, and (v) patient preferences. Importantly, these factors are considered within a regulatory framework that imposes certain overarching formulary requirements. ..First, Part D plans must ensure that their formulary designs are nondiscriminatory. CMS considers several criteria when assessing whether a formulary is nondiscriminatory. CMS may presumptively approve formulary designs which align with the United States Pharmacopoeia's (USP) Medicare Model Guidelines (MMGs) based on the view that the MMGs reflect a scientifically and-clinically-based taxonomy developed by an independent expert body without a vested financial interest in the Part D program. The MMGs are also important because they provide a guiding framework for Part D plans to use when determining therapeutic alternatives. The MMGs group drugs into categories and classes. These categories and classes generally encompass the universe of potential therapeutic alternatives for a given medical condition. This means that Part D plans can use the MMGs to identify the range of therapeutic alternatives to consider when developing their formularies...Second, Part D plans must provide an adequate formulary, which among other things, means including at least two Part D drugs within a particular category or class of Part D drugs. This minimum formulary standard helps ensure a wide range of treatment options for enrollees, even if they have complex or rare medical conditions. Additionally, this requirement promotes patient choice and competition among drug manufacturers because the ability for patients to access alternative treatments incentivizes drug manufacturers to lower prices and innovate. The requirement to include at least two drugs per category or class helps to ensure that patients with a given medical condition have at least two formulary treatment options available to them, even if there are few therapeutic alternatives. This requirement is important because it prevents Part D plans from excluding entire categories or classes of drugs from their formularies...Third, Part D plans must consider cost sharing in the development of formularies. For example, CMS could raise concerns about formularies that place drugs on high cost-sharing tiers without placing therapeutic alternatives in preferable positions. CMS has also expressed concerns about "adverse tiering" where a plan sponsor assigns most or all drugs in the same therapeutic class needed to treat a specific chronic, high-cost medical condition to a high cost-sharing tier. In short, Part D plans must consider the enrollee's share of costs for a particular drug when considering therapeutic alternatives...PCMA encourages CMS to identify therapeutic alternatives for the Medicare Drug Price Negotiation Program in the same way that Part D plans do for their formularies. This would ensure consistency in process across two closely related programs and avoid introducing multiple, confusing standards for the same underlying</p> |
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|  |  | <p>definitional term. At the very least, aligning the selection of therapeutic alternatives under the Medicare Drug Price Negotiation Program with Part D formulary submissions would give Part D plans some assurance that CMS's assessment of their formulary submissions will not be affected by CMS's own process of selecting therapeutic alternatives...II. CMS's identification of therapeutic alternatives for the Medicare Drug Price Negotiation Program should not compromise the agency's evaluation of the adequacy of Part D plan formulary design, ensuring that Medicare beneficiaries continue to have access to a broad range of affordable prescription drugs...PCMA acknowledges that CMS's identification of therapeutic alternatives under the Medicare Drug Price Negotiation Program is required by law and essential for successful drug pricing negotiations. As stated above, we urge CMS to attempt to align its selection of therapeutic alternatives with how Part D plans select therapeutic alternatives...That being said, it is important to recognize that the exercise of selecting therapeutic alternatives for the Medicare Drug Price Negotiation Program and the Part D program, while overlapping in some areas, are ultimately distinct. Selecting therapeutic alternatives for the Medicare Drug Price Negotiation Program requires unique considerations that are not fully applicable to how Part D plans identify and leverage therapeutic alternatives for formulary development. Accordingly, we do not expect CMS to perfectly align itself with Part D plan sponsor methodologies for selecting therapeutic alternatives. ..First, therapeutic alternatives are a statutory feature of the Medicare Drug Price Negotiation Program. CMS selects therapeutic alternatives when negotiating pricing for selected drugs because the statute requires the agency to do so. Even if the statute did not require CMS to identify therapeutic alternatives, CMS would likely need to do so because it supports the agency in carrying out its statutory mandate to negotiate a "maximum fair price" (MFP) with manufacturers. Importantly, the MFP applies in a vacuum without regards to affordability and relative competitiveness with other drugs that a beneficiary may access...By contrast, while Part D plans are required to select therapeutic alternatives for formulary submissions, Part D plans select therapeutic alternatives based on a delicate balance between clinical comparability, cost-effectiveness, and beneficiary access. Unlike CMS, which is required to focus on a single drug in isolation when assessing therapeutic alternatives, Part D plans, PBMs, and their pharmacy and therapeutics (P&amp;T) committees are tasked with developing comprehensive formularies that holistically meet the complex needs of their enrollees. Part D plans must, already, cover selected drugs on their formularies under the statute, and CMS's interpretation worryingly suggests that such coverage may also involve a preferred status designation. Additional indirect restrictions on formulary design stemming from CMS's evaluation criteria under the Medicare Drug Price Negotiation Program could significantly hamper Part D plans' ability to offer competitive plan designs. In light of the comprehensive considerations that Part D plans must consider in developing formularies, CMS must ensure plans retain flexibility to adequately weigh all of these factors when developing formularies, including identifying therapeutic alternatives...Second, CMS's selection of therapeutic alternatives is a one-time event, done solely to determine the MFP for a selected drug. Once the MFP is determined, the drug's therapeutic alternatives play no further role in how Medicare beneficiaries access the selected drug...In contrast, a Part D plan sponsor's selection of therapeutic alternatives is used in multiple ways, including</p> |
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formulary design, coverage determination, tiering exceptions, and Part D appeals. This means that Part D plans must carefully consider all potential scenarios in which their selection of therapeutic alternatives may be challenged...Third, CMS's identification of therapeutic alternatives for purposes of the Drug Price Negotiation Program is nonpublic. CMS indicates in the Revised Guidance for the Medicare Drug Price Negotiation Program that the agency will not unilaterally disclose any information pertaining to its negotiations with manufacturers, including the therapeutic alternatives identified for such negotiations. As a result, Part D plans do not have access to the therapeutic alternatives that CMS identifies for selected drugs. It would be unfair and arbitrary for CMS to evaluate Part D plan formulary submissions, including the identification of therapeutic alternatives contained in the submission, on a criteria that CMS never releases to the public. Formulary guidelines like the USP Medicare Model Guidelines provide a more predictable basis for administering a prescription drug benefit than nonpublic information. ..In short, while we urge CMS to align its methodology for selecting therapeutic alternatives as much as possible with Part D plans, we also request that CMS clarify that the therapeutic alternatives considered in the Medicare Drug Price Negotiation Program are distinct from the therapeutic alternatives that Part D plans must identify for purposes of formulary submissions and the overall administration of the prescription drug benefit. This will help ensure that Medicare beneficiaries continue to have access to a broad range of affordable prescription drugs. CMS can do this via an HPMS memo to Part D plans...III. Part D plans may continue to identify therapeutic alternatives in enrollee communications consistent with existing practices, regardless of CMS's identification of therapeutic alternatives for Medicare Drug Price Negotiation Program. ..Apart from formulary development, the issue of a drug's therapeutic alternatives also has implications on communications Part D sponsors are required to provide to enrollees. The Annual Notice of Change (ANOC) describes any changes to the plan's benefits, formularies, and costs for the upcoming year. The Evidence of Coverage (EOC) document describes the plan's benefits, coverage, and exclusions. Real-time benefit tools (RTBT) provide prescribers with information at the point-of-care on formulary and benefit information (including cost, formulary alternatives, and utilization management requirements). The monthly Explanation of Benefits (EOB) must include lower cost alternatives. ..While Part D plans are not required to include information about therapeutic alternatives in the ANOC or EOC, many voluntarily do so to help enrollees make informed decisions about their prescription drug coverage. This information is especially valuable for enrollees and prospective enrollees to fully understand the different treatment options available to them based on their unique circumstances. This transparency also promotes competition among Part D plans, as enrollees can better assess which plans are best for them. ..The RTBT and EOB rules have granted plans latitude in selecting which therapeutic alternatives would be displayed. CMS has stated that the "purpose of the beneficiary RTBT is to better inform beneficiaries about alternative medications," and thus, CMS allows "part D sponsors flexibility in implementing this requirement." For the EOB, CMS requires Part D sponsors to include lower-cost therapeutic alternatives but does not impose any specific requirements on plans on how they should identify those therapeutic alternatives...In summary, while Part D plans are required to communicate certain information to enrollees about therapeutic alternatives, CMS



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provides plans with significant flexibility in the selection of those therapeutic alternatives. As such, CMS should explicitly clarify that the information on therapeutic alternatives that Part D plans choose to communicate to enrollees in required enrollee communications to beneficiaries and other regulatory requirements is not affected by CMS's selection of therapeutic alternatives for purposes of the Medicare Drug Price Negotiation Program.

Hyperlink to  
Table/Charts/Graphs -  
Additional Materials for  
Question 28  
Evidence Submitted include  
a cost-effectiveness  
measure?

What type of Evidence is  
shown?

Response to Question 29

Hyperlink to Citation -  
Additional Materials for  
Question 29

Question 29:  
Comparative  
Effectiveness  
on Specific  
Populations

Hyperlink to  
Table/Charts/Graphs -  
Additional Materials for  
Question 29

Evidence Submitted include  
a cost-effectiveness  
measure?

What type of Evidence is  
shown?

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| Question 30:<br>Addressing<br>Unmet<br>Medical<br>Needs | Response to Question 30  |          |
|   | Hyperlink to Citation -<br>Additional Materials for<br>Question 30               |          |
|   | Hyperlink to<br>Table/Charts/Graphs -<br>Additional Materials for<br>Question 30 |          |
|   | Evidence Submitted include<br>a cost-effectiveness<br>measure?                   |          |
|   | What type of Evidence is<br>shown?   |          |
| Question 31:<br>Patient and<br>Caregiver<br>Experience  | Response to Question 31  |          |
| Question 32:<br>Executive<br>Summary                    | Response to Question 32  |          |



## Answers to Question #28 for Public Submission

The Pharmaceutical Care Management Association (PCMA) appreciates the opportunity to submit comments regarding the therapeutic alternatives for Valsartan/Sacubitrilat. Our members help administer the Part D prescription drug benefit on behalf of many Part D plan sponsors, and a central component of that function is the identification of therapeutic alternatives to develop comprehensive prescription drug formularies consistent with applicable statutory, regulatory, and clinical requirements, including ensuring formularies are not discriminatory.

In general, while we understand that CMS cannot disclose the specifics of their negotiations with manufacturers of selected drugs, we believe the public is best served by CMS disclosing as much about this process as possible, and otherwise aligning its methodology for selecting therapeutic alternatives with how Part D plans select therapeutic alternatives. Our comments focus on emphasizing the differences between identifying therapeutic alternatives for purposes of the Medicare Drug Price Negotiation Program, and the role that the identification of therapeutic alternatives plays under the Medicare Part D program's formulary standards and enrollee communication requirements. PCMA has three main points:

1. As a general principle, CMS should identify therapeutic alternatives under the Medicare Drug Price Negotiation Program consistent with the guardrails that apply to Part D plan sponsors when identifying therapeutic alternatives for the Part D program.
2. CMS should clarify in an HPMS memo to Part D plans that CMS's identification of therapeutic alternatives for the Medicare Drug Price Negotiation Program will not impact the agency's existing approach towards evaluating Part D formulary design for compliance with Part D formulary requirements.
3. CMS should clarify in an HPMS memo that Part D plans retain discretion on how to communicate therapeutic alternatives to enrollees, and that CMS's identification of therapeutic alternatives for purposes of the Medicare Drug Price Negotiation Program will not affect these enrollee communications.

We discuss these issues in more detail below.

### **I. CMS should identify therapeutic alternatives under the Medicare Drug Price Negotiation Program consistent with the guardrails that apply to Part D plan sponsors when identifying therapeutic alternatives for their formulary submissions.**

Currently, Part D plan sponsors consider a variety of factors when identifying therapeutic alternatives for their formulary submissions, including but not limited to (i) clinical effectiveness, (ii) safety, (iii) price, (iv) availability, and (v) patient preferences. Importantly, these factors are considered within a regulatory framework that imposes certain overarching formulary requirements.

First, Part D plans must ensure that their formulary designs are nondiscriminatory.<sup>1</sup> CMS considers several criteria when assessing whether a formulary is nondiscriminatory. CMS may presumptively approve formulary designs which align with the United States Pharmacopoeia's (USP) Medicare Model Guidelines (MMGs) based on the view that the MMGs reflect a

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<sup>1</sup> See 42 C.F.R. § 423.272(b)(2).

scientifically and-clinically-based taxonomy developed by an independent expert body without a vested financial interest in the Part D program. The MMGs are also important because they provide a guiding framework for Part D plans to use when determining therapeutic alternatives. The MMGs group drugs into categories and classes. These categories and classes generally encompass the universe of potential therapeutic alternatives for a given medical condition. This means that Part D plans can use the MMGs to identify the range of therapeutic alternatives to consider when developing their formularies.

Second, Part D plans must provide an adequate formulary, which among other things, means including at least two Part D drugs within a particular category or class of Part D drugs.<sup>2</sup> This minimum formulary standard helps ensure a wide range of treatment options for enrollees, even if they have complex or rare medical conditions. Additionally, this requirement promotes patient choice and competition among drug manufacturers because the ability for patients to access alternative treatments incentivizes drug manufacturers to lower prices and innovate. The requirement to include at least two drugs per category or class helps to ensure that patients with a given medical condition have at least two formulary treatment options available to them, even if there are few therapeutic alternatives. This requirement is important because it prevents Part D plans from excluding entire categories or classes of drugs from their formularies.

Third, Part D plans must consider cost sharing in the development of formularies. For example, CMS could raise concerns about formularies that place drugs on high cost-sharing tiers without placing therapeutic alternatives in preferable positions.<sup>3</sup> CMS has also expressed concerns about "adverse tiering" where a plan sponsor assigns most or all drugs in the same therapeutic class needed to treat a specific chronic, high-cost medical condition to a high cost-sharing tier.<sup>4</sup> In short, Part D plans must consider the enrollee's share of costs for a particular drug when considering therapeutic alternatives.

PCMA encourages CMS to identify therapeutic alternatives for the Medicare Drug Price Negotiation Program in the same way that Part D plans do for their formularies. This would ensure consistency in process across two closely related programs and avoid introducing multiple, confusing standards for the same underlying definitional term. At the very least, aligning the selection of therapeutic alternatives under the Medicare Drug Price Negotiation Program with Part D formulary submissions would give Part D plans some assurance that CMS's assessment of their formulary submissions will not be affected by CMS's own process of selecting therapeutic alternatives.

**II. CMS's identification of therapeutic alternatives for the Medicare Drug Price Negotiation Program should not compromise the agency's evaluation of the adequacy of Part D plan formulary design, ensuring that Medicare beneficiaries continue to have access to a broad range of affordable prescription drugs.**

PCMA acknowledges that CMS's identification of therapeutic alternatives under the Medicare Drug Price Negotiation Program is required by law and essential for successful drug pricing

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<sup>2</sup> *Id.* at §

<sup>3</sup> § 30.2.7, Chapter 6, Medicare Prescription Drug Manual ("The CMS review will focus on identifying drug categories that may substantially discourage enrollment of certain beneficiaries by placing drugs in non-preferred tiers in the absence of commonly used therapeutically similar drugs in more preferred positions.").

<sup>4</sup> 87 Fed. Reg. 27208, 27303 (May 6, 2022).

negotiations. As stated above, we urge CMS to attempt to align its selection of therapeutic alternatives with how Part D plans select therapeutic alternatives.

That being said, it is important to recognize that the exercise of selecting therapeutic alternatives for the Medicare Drug Price Negotiation Program and the Part D program, while overlapping in some areas, are ultimately distinct. Selecting therapeutic alternatives for the Medicare Drug Price Negotiation Program requires unique considerations that are not fully applicable to how Part D plans identify and leverage therapeutic alternatives for formulary development.<sup>5</sup> Accordingly, we do not expect CMS to perfectly align itself with Part D plan sponsor methodologies for selecting therapeutic alternatives.

First, therapeutic alternatives are a statutory feature of the Medicare Drug Price Negotiation Program. CMS selects therapeutic alternatives when negotiating pricing for selected drugs because the statute *requires* the agency to do so. Even if the statute did not require CMS to identify therapeutic alternatives, CMS would likely need to do so because it supports the agency in carrying out its statutory mandate to negotiate a "maximum fair price" (MFP) with manufacturers. Importantly, the MFP applies in a vacuum without regards to affordability and relative competitiveness with other drugs that a beneficiary may access.

By contrast, while Part D plans are required to select therapeutic alternatives for formulary submissions, Part D plans select therapeutic alternatives based on a delicate balance between clinical comparability, cost-effectiveness, and beneficiary access. Unlike CMS, which is required to focus on a single drug in isolation when assessing therapeutic alternatives, Part D plans, PBMs, and their pharmacy and therapeutics (P&T) committees are tasked with developing comprehensive formularies that holistically meet the complex needs of their enrollees. Part D plans must, already, cover selected drugs on their formularies under the statute,<sup>6</sup> and CMS's interpretation worryingly suggests that such coverage may also involve a preferred status designation.<sup>7</sup> Additional indirect restrictions on formulary design stemming from CMS's evaluation criteria under the Medicare Drug Price Negotiation Program could significantly hamper Part D plans' ability to offer competitive plan designs. In light of the comprehensive considerations that Part D plans must consider in developing formularies, CMS must ensure plans retain flexibility to adequately weigh all of these factors when developing formularies, including identifying therapeutic alternatives.

Second, CMS's selection of therapeutic alternatives is a one-time event, done solely to determine the MFP for a selected drug. Once the MFP is determined, the drug's therapeutic alternatives play no further role in how Medicare beneficiaries access the selected drug.

In contrast, a Part D plan sponsor's selection of therapeutic alternatives is used in multiple ways, including formulary design, coverage determination, tiering exceptions, and Part D appeals. This means that Part D plans must carefully consider all potential scenarios in which their selection of therapeutic alternatives may be challenged.

Third, CMS's identification of therapeutic alternatives for purposes of the Drug Price Negotiation Program is nonpublic. CMS indicates in the Revised Guidance for the Medicare Drug Price

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<sup>5</sup> See 42 C.F.R. § 423.128(d)(4)(ii).

<sup>6</sup> Social Security Act § 1860D-4(b)(3)(I).

<sup>7</sup> See § 110, Medicare Drug Price Negotiation Program: Revised Guidance (June 30, 2023), <https://www.cms.gov/files/document/revised-medicare-drug-price-negotiation-program-guidance-june-2023.pdf>.

Negotiation Program that the agency will not unilaterally disclose any information pertaining to its negotiations with manufacturers, including the therapeutic alternatives identified for such negotiations. As a result, Part D plans do not have access to the therapeutic alternatives that CMS identifies for selected drugs. It would be unfair and arbitrary for CMS to evaluate Part D plan formulary submissions, including the identification of therapeutic alternatives contained in the submission, on a criteria that CMS never releases to the public. Formulary guidelines like the USP Medicare Model Guidelines provide a more predictable basis for administering a prescription drug benefit than nonpublic information.

In short, while we urge CMS to align its methodology for selecting therapeutic alternatives as much as possible with Part D plans, we also request that CMS clarify that the therapeutic alternatives considered in the Medicare Drug Price Negotiation Program are distinct from the therapeutic alternatives that Part D plans must identify for purposes of formulary submissions and the overall administration of the prescription drug benefit. This will help ensure that Medicare beneficiaries continue to have access to a broad range of affordable prescription drugs. CMS can do this via an HPMS memo to Part D plans.

**III. Part D plans may continue to identify therapeutic alternatives in enrollee communications consistent with existing practices, regardless of CMS's identification of therapeutic alternatives for Medicare Drug Price Negotiation Program.**

Apart from formulary development, the issue of a drug's therapeutic alternatives also has implications on communications Part D sponsors are required to provide to enrollees. The Annual Notice of Change (ANOC) describes any changes to the plan's benefits, formularies, and costs for the upcoming year. The Evidence of Coverage (EOC) document describes the plan's benefits, coverage, and exclusions. Real-time benefit tools (RTBT) provide prescribers with information at the point-of-care on formulary and benefit information (including cost, formulary alternatives, and utilization management requirements).<sup>8</sup> The monthly Explanation of Benefits (EOB) must include lower cost alternatives.<sup>9</sup>

While Part D plans are not required to include information about therapeutic alternatives in the ANOC or EOC, many voluntarily do so to help enrollees make informed decisions about their prescription drug coverage. This information is especially valuable for enrollees and prospective enrollees to fully understand the different treatment options available to them based on their unique circumstances. This transparency also promotes competition among Part D plans, as enrollees can better assess which plans are best for them.

The RTBT and EOB rules have granted plans latitude in selecting which therapeutic alternatives would be displayed. CMS has stated that the "purpose of the beneficiary RTBT is to better inform beneficiaries about alternative medications," and thus, CMS allows "part D sponsors flexibility in implementing this requirement."<sup>10</sup> For the EOB, CMS requires Part D sponsors to include lower-cost therapeutic alternatives but does not impose any specific requirements on plans on how they should identify those therapeutic alternatives.

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<sup>8</sup> § 119, Title I, Division CC, Consolidated Appropriations Act, 2021, Pub. L. No. 117-328 (amending section 1860D-4); *see also* 86 Fed. Reg. 5864, 5868 (Jan. 19, 2021).

<sup>9</sup> 42 C.F.R. 423.138(e)(5).

<sup>10</sup> 86 Fed. Reg. 5864, (May 6, 2022).



In summary, while Part D plans are required to communicate certain information to enrollees about therapeutic alternatives, CMS provides plans with significant flexibility in the selection of those therapeutic alternatives. As such, CMS should explicitly clarify that the information on therapeutic alternatives that Part D plans choose to communicate to enrollees in required enrollee communications to beneficiaries and other regulatory requirements is not affected by CMS's selection of therapeutic alternatives for purposes of the Medicare Drug Price Negotiation Program.