



Maximum Fair Price (MFP) Explanation for Entresto

Introduction

In August 2022, President Biden signed the Inflation Reduction Act of 2022 (IRA) (P.L. 117-169) into law. For the first time, the law provides Medicare with the ability to directly negotiate the prices of certain high expenditure, single source drugs without generic or biosimilar competition. On March 15, 2023, the Centers for Medicare & Medicaid Services (CMS) issued [initial guidance](#) for the Medicare Drug Price Negotiation Program (the “Negotiation Program”), including requests for public comment on key elements. On June 30, 2023, CMS issued [revised guidance](#) detailing the requirements and parameters of the Negotiation Program for the first cycle of negotiations.¹ CMS engaged in negotiations with participating manufacturers between October 1, 2023 and August 1, 2024. These negotiations resulted in agreements establishing prices (which the IRA refers to as “maximum fair prices” or “MFPs”) that will be effective beginning in 2026 (the first cycle of negotiations is referred to as negotiations for “initial price applicability year 2026” because any agreed-upon prices will be effective in 2026). CMS published the agreed-upon MFPs on August 15, 2024.

The MFP explanation for Entresto for the agreed-upon MFP that resulted from the negotiations for initial price applicability year 2026 with Novartis Pharms Corp, the manufacturer of Entresto (the “Primary Manufacturer”), provides information about the negotiations for Entresto. This information includes CMS’ perspective on the data considered that had the greatest impact in CMS’ determination of offers and consideration of counteroffers during the negotiation process through which the parties reached agreement on an MFP.² In some respects, the Primary Manufacturer had a different perspective on the relevant data. The parties to the negotiation had productive exchanges during the negotiation meetings described below in which they discussed their respective views, and these exchanges resulted in the exchange of offer(s) and counteroffer(s) among the parties and, ultimately, an agreed-upon MFP for Entresto.

On the basis of the factors described below and the related considerations and evidence, CMS negotiated with the Primary Manufacturer in good faith and consistent with the requirements of the law on behalf of people with Medicare and the Medicare program. Throughout the negotiation process and in accordance with the IRA, CMS’ goal was to achieve agreement with the Primary Manufacturer on the lowest possible MFP for Entresto that would be consistent with the process defined in the IRA for these price negotiations. CMS believes that the agreed-upon MFP achieves this aim. The negotiation process

¹ The [Medicare Drug Price Negotiation Program: Revised Guidance, Implementation of Sections 1191 – 1198 of the Social Security Act for Initial Price Applicability Year 2026](#), is referred to throughout this document as the revised guidance.

² Section 1195(a)(2) of the Social Security Act (the “Act”) requires CMS to publish an explanation for the MFP with respect to the factors as applied under section 1194(e) for each selected drug. The MFP explanation is discussed in section 60.6.1 of the [revised guidance](#).

ended in both parties agreeing to an MFP of \$295.00 for Entresto by the conclusion of the negotiation period on August 1, 2024.³ The agreed-upon MFP is set to take effect on January 1, 2026.

The MFP explanation contains the following components:

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MFP Explanation Narrative for Entresto

Summary of the Negotiation Process

CMS followed the negotiation process laid out in the IRA and in the revised guidance. On August 29, 2023, CMS announced the 10 selected drugs for the first cycle of negotiations, which included Entresto. The Primary Manufacturers of the selected drugs signed agreements to participate in the Negotiation Program by the deadline in the IRA of October 1, 2023 and submitted information on the selected drugs by the deadline in the IRA of October 2, 2023.

CMS collected relevant data from numerous sources, such as written submissions from the Primary Manufacturers and other interested parties in response to an information collection request issued for the Negotiation Program (referred to as the “Negotiation Program information collection request” throughout this document), feedback from patient-focused listening sessions, meetings between CMS and the Primary Manufacturers to discuss the information submitted, and CMS’ literature review.⁴

Using the information collected, CMS then developed initial offers for the selected drugs, which were based on the factors outlined in the IRA for CMS’ determination of offers and which CMS developed in accordance with the process described in the revised guidance.⁵ As required by the IRA, CMS’ initial offers each included a concise justification on the range of evidence and other information within the negotiation factors that CMS found compelling during the development of the initial offer. The Primary Manufacturers each responded by declining CMS’ initial offer and providing a written counteroffer and justification for such offer, including considerations based on the negotiation factors.

³ The MFP is expressed as the price per 30-days equivalent supply. See section 60.1 of the [revised guidance](#) and the [Negotiated Prices for Initial Price Applicability Year 2026 Fact Sheet](#) for additional information.

⁴ 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.

⁵ Section 1194(e) of the Act requires CMS to consider certain data as the basis for all offers and counteroffers in the negotiation. These data, which are referred to in this document as the “negotiation factors,” are discussed in more detail later in this document. More information on the negotiation factors is also available in sections 50, 60.3 and 60.4 of the [revised guidance](#). CMS’ process for developing the initial offers is described in section 60.3 of the revised guidance.

CMS considered each counteroffer proposed by the Primary Manufacturers and declined each counteroffer. CMS and each Primary Manufacturer then held three negotiation meetings. These meetings included extensive discussion of the negotiation factors, including any new information consistent with the factors that may have become available about the selected drugs or therapeutic alternatives, CMS' initial offer and the Primary Manufacturer's written counteroffer, and, in some cases, additional proposals for an MFP.

Across the first cycle of negotiations for all ten selected drugs, more than 50 revised offers or counteroffers were proposed by CMS or a Primary Manufacturer, not including the ten initial offers CMS made and the ten written counteroffers provided by Primary Manufacturers. During the negotiation meetings, CMS revised its initial offer for each selected drug upwards at least once in response to the discussions with the Primary Manufacturer. While many of the details of the negotiations are confidential between CMS and each Primary Manufacturer, the frequency of revised offers and counteroffers in the first cycle of negotiations indicates the robustness of the negotiations that occurred for each of the ten drugs. CMS' approach to its negotiations with each Primary Manufacturer turned on the particular details relevant to each selected drug and was sensitive to the issues raised during the course of CMS' conversations with the Primary Manufacturer. CMS anticipates this drug-specific approach will continue to inform CMS' negotiations with participating manufacturers in future cycles of negotiation.

Overall, in six of ten negotiations CMS moved more than the Primary Manufacturer during the meetings and for the final offer (if applicable) prior to reaching agreement, and in four of ten negotiations the Primary Manufacturer moved more than CMS prior to reaching agreement. For five of the selected drugs, this process of exchanging revised offers and counteroffers resulted in CMS and the Primary Manufacturer reaching an agreement on a negotiated price for the selected drug in association with a negotiation meeting. In four of these cases, CMS accepted a revised counteroffer proposed by the Primary Manufacturer. For the remaining five selected drugs, CMS sent a written final offer to the Primary Manufacturer, consistent with the process described in the revised guidance, and in each instance, the Primary Manufacturer accepted CMS' offer on or before the statutory deadline. Throughout the negotiation process, CMS and the Primary Manufacturers exchanged perspectives about a range of topics related to the negotiation factors, and while the parties did not always agree, CMS appreciated the Primary Manufacturers' engagement.

A detailed timeline of the negotiation process for Entresto is below.

- August 29, 2023: CMS announced the 10 selected drugs for initial price applicability year 2026
- October 1, 2023: Deadline for the Primary Manufacturer to sign an agreement to participate in the Negotiation Program
- October 2, 2023: Deadline for the Primary Manufacturer and the public to submit information related to Entresto in response to the Negotiation Program information collection request
- October 26, 2023: CMS met with the Primary Manufacturer regarding its response to the Negotiation Program information collection request
- November 1, 2023: CMS held a patient-focused listening session for Entresto
- February 1, 2024: CMS provided the Primary Manufacturer with CMS' initial offer
- February 29, 2024: The Primary Manufacturer rejected CMS' initial offer and provided CMS with a counteroffer
- March 29, 2024: CMS rejected the Primary Manufacturer's counteroffer and invited the Primary Manufacturer to a negotiation meeting
- May 3, 2024: CMS and the Primary Manufacturer met for the first negotiation meeting

- May 21, 2024: CMS and the Primary Manufacturer met for the second negotiation meeting
- June 18, 2024: CMS and the Primary Manufacturer met for the third negotiation meeting
- August 1, 2024: The negotiation period ended
- August 15, 2024: MFP of \$295.00 was published

Indications for Entresto

Entresto is a combination of a neprilysin inhibitor, sacubitril, and an angiotensin II receptor blocker, valsartan, that works to relax blood vessels, to decrease sodium and fluid in the body, to improve heart function and to reduce associated risks in patients with heart failure. Heart failure may be classified based on a measurement of how much blood is pumped out of the heart's left ventricle with each beat, called the left ventricular ejection fraction (LVEF). Heart failure may be classified by LVEF measurements, including as heart failure with reduced ejection fraction (HFrEF) or heart failure with preserved ejection fraction (HFpEF).⁶

For Entresto, CMS included the following indications in its assessment⁷:

Description of indication	Terminology used in this document
<ul style="list-style-type: none"> • To reduce the risk of cardiovascular (CV) death and hospitalization for heart failure (HF) in adult patients with chronic HF. • For the treatment of symptomatic HF with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older. Entresto reduces NT-proBNP and is expected to improve CV outcomes. 	HF

Table 1. NT-proBNP = N-terminal pro-brain natriuretic peptide, a protein that is made by the heart and blood vessels, which is elevated in patients with heart failure. For purposes of CMS' consideration of indications for Entresto, CMS grouped certain indications using the terminology as shown in this table. CMS' use of the terms listed here does not alter the FDA-approved indications for Entresto.

Factors Applied

Consistent with the IRA, CMS considered certain negotiation factors as the basis for determining all offers and counteroffers during the negotiation process.

The following negotiation factors are referred to in this document as "manufacturer-specific data"⁸:

⁶ To compose this brief description, CMS used various sources, including MedlinePlus, a free online health information resource for patients and the general public. MedlinePlus is a service of the National Library of Medicine (NLM), a part of the U.S. National Institutes of Health (NIH). For more information about any drugs or conditions mentioned in this document, MedlinePlus can be accessed at: <https://medlineplus.gov/>.

⁷ CMS' process for identifying indications for a selected drug was to identify the FDA-approved indication(s) not otherwise excluded from coverage or otherwise restricted under section 1860D-2(e)(2) of the Act, using prescribing information approved by the FDA for the selected drug, in accordance with section 1194(e)(2)(B) of the Act. CMS considered off-label use when identifying indications if such use was included in nationally recognized, evidence-based guidelines and recognized in CMS-approved Part D compendia. CMS included indications that met these criteria during the negotiation period. Indications newly approved by FDA or included in nationally recognized, evidence-based guidelines and recognized in CMS-approved Part D compendia after the end of the negotiation period were not included.

⁸ These factors are listed at section 1194(e)(1) of the Act.

- Research and development (R&D) costs of the Primary Manufacturer for Entresto and the extent to which the Primary Manufacturer has recouped R&D costs;
- Current unit costs of production and distribution of Entresto;
- Prior Federal financial support for novel therapeutic discovery and development with respect to Entresto;
- Data on pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals for New Drug Applications and Biologics License Applications for Entresto;⁹ and
- Market data and revenue and sales volume data for Entresto in the United States (U.S.).

The following negotiation factors are referred to in this document as “evidence about Entresto and therapeutic alternatives to Entresto”¹⁰:

- The extent to which Entresto represents a therapeutic advance as compared to existing therapeutic alternatives and the costs of such existing therapeutic alternatives;
- Prescribing information approved by the FDA for Entresto and therapeutic alternatives to Entresto;
- Comparative effectiveness of Entresto and therapeutic alternatives to Entresto, taking into consideration the effects of Entresto and therapeutic alternatives to Entresto on specific populations, such as individuals with disabilities, the elderly, the terminally ill, children, and other patient populations; and
- The extent to which Entresto and therapeutic alternatives to Entresto address unmet medical needs for a condition for which treatment or diagnosis is not addressed adequately by available therapy.

The below sections describe how CMS considered and applied these factors during the negotiation process. CMS considered these factors, taking into account all data in totality during the negotiation process.

CMS and the Primary Manufacturer did not always agree on the information presented below, and the Primary Manufacturer was not restricted to consideration of these factors during the negotiation process but was free to discuss any topics with CMS it deemed relevant to its consideration of offer(s) and counteroffer(s) for Entresto.

Manufacturer-Specific Data

CMS considered the information submitted by the Primary Manufacturer related to the manufacturer-specific data factors. These factors include R&D costs and the extent to which the Primary Manufacturer has recouped R&D costs, current unit costs of production and distribution, prior Federal financial support, data on pending and approved patents and exclusivities recognized by the FDA, and market

⁹ New Drug Applications are approved under section 505(c) of the Federal Food, Drug, and Cosmetic Act and Biologics License Applications are approved under section 351(a) of the Public Health Service Act.

¹⁰ These factors are listed at section 1194(e)(2) of the Act. In accordance with section 1194(e)(2) and section 1182(e) of Title XI of the Act, CMS did not use evidence from comparative clinical effectiveness research in a manner that treats extending the life of an individual who is elderly, disabled, or terminally ill as of lower value than extending the life of an individual who is younger, non-disabled, or not terminally ill, and, consistent with section 1182(e) of Title XI of the Act, did not use quality adjusted life years (QALYs).

data, including revenue and sales volume data for the drug in the United States. CMS considered these factors in totality, as part of its application of the negotiation factors during the negotiation process.

The Primary Manufacturer provided CMS with information for each of these factors in response to the Negotiation Program information collection request.¹¹ For R&D costs, CMS requested information separated into various categories of costs related to R&D, including acquisition costs, pre-clinical research costs, post-Investigational New Drug costs, costs of failed or abandoned products related to Entresto, and other allowable direct costs. CMS also requested the global and U.S. total lifetime net revenue for Entresto to provide insight into the extent to which the Primary Manufacturer has recouped R&D costs. CMS requested current average unit costs of production for Entresto and current average unit costs of distribution for Entresto separately, as well as a description of the methodology the Primary Manufacturer used to estimate such costs. For information related to prior Federal financial support, CMS requested the total amount of Federal financial support received, as well as a breakdown by various types of financial support, like tax credits and National Institutes of Health funding. CMS requested information on patents, both expired and unexpired, issued by the U.S. Patent and Trademark Office, patent applications, regulatory exclusivity periods, and active and pending FDA applications and approvals. For market data, CMS requested information about the prices for Entresto and volume dispensed for other payers in the U.S. market, including commercial payers (e.g., the U.S. commercial average net price), Medicaid (Medicaid Best Price), and other Federal payers (the Federal supply schedule price and the Big Four price).

Throughout the negotiation process, CMS holistically considered the information submitted by the Primary Manufacturer related to the manufacturer-specific data negotiation factors for the purpose of negotiating an MFP for Entresto. For example, CMS applied information on prices for Entresto available to other payers in the U.S. market and how they compared to any offers or counteroffers when considering whether a potential price was consistent with CMS' aim to arrive at an agreement on the lowest possible MFP. The totality of CMS' application of these factors, in conjunction with application of the factors described below, informed CMS' negotiation of the MFP with the Primary Manufacturer.

Evidence about Entresto and Therapeutic Alternatives to Entresto

CMS considered information related to the negotiation factors regarding evidence about Entresto and therapeutic alternatives to Entresto. CMS' holistic consideration of clinical benefit included evidence from sources such as: pivotal clinical trials, pre-specified subgroup analyses, clinical practice guidelines, expert consensus statements, comparative clinical evidence, published literature reviews, real-world evidence, and FDA prescription drug labeling, among others. CMS evaluated the evidence based on a variety of considerations, including relevance and credibility, giving priority to well-designed and well-conducted studies, as stated in the revised guidance.¹² In general, CMS prioritized direct comparative

¹¹ In accordance with the revised guidance, CMS treats R&D costs and the extent to which they are recouped, unit costs of production and distribution, pending patent applications, and market, revenue, and sales volume data as proprietary, unless the information that is provided to CMS is already publicly available. For more information, see section 40.2.1 of the [revised guidance](#).

¹² In section 50.2 of the [revised guidance](#), CMS stated, "When reviewing the literature from the public and manufacturer submissions as well as literature from CMS' review, CMS will consider the source, rigor of the study methodology, current relevance to the selected drug and its therapeutic alternative(s), whether the study has been through peer review, study limitations, degree of certainty of conclusions, risk of bias, study time horizons, generalizability, study population, and relevance to the negotiation factors listed in section 1194(e)(2) of the Act to ensure the integrity of the contributing data within the negotiation process. CMS will prioritize research, including

evidence (e.g., head-to-head randomized controlled trials) when available. CMS also reviewed mixed and/or indirect treatment comparisons (e.g., network meta-analyses) when available and real-world evidence (e.g., observational studies) when available as part of its holistic assessment of comparative evidence.

In addition to information from the Primary Manufacturer, CMS received information from the public, including from patients during the patient-focused listening session held by CMS on November 1, 2023.¹³ Patient input was important to CMS' consideration of the evidence about Entresto and therapeutic alternatives to Entresto, including to help identify outcomes of interest for patients and to understand additional considerations such as the drug's impact on patients' daily lives. For example, speakers at the patient-focused listening session shared that Entresto helped to prevent hospitalizations for HF, to alleviate symptoms such as swelling and fatigue, and to allow increased engagement in activities of daily living. These were some considerations among the many that informed CMS' understanding of the factors regarding evidence about Entresto and its therapeutic alternatives. Throughout all of the patient-focused listening sessions for the first cycle of negotiations, speakers provided insight on the importance of affordability and access, which provided CMS helpful context for the speakers' described experiences.

Therapeutic Alternatives

The IRA directs CMS to compare Entresto to therapeutic alternatives in its determination of offers and consideration of counteroffers for Entresto.¹⁴ In the revised guidance, CMS defines a therapeutic alternative for the first cycle of negotiations as a pharmaceutical product that is clinically comparable to the selected drug.¹⁵

Importantly, use of the term “therapeutic alternative” in this MFP explanation is limited to the purposes and definition outlined in the IRA and the revised guidance. Use of this term does not suggest that CMS believes such drugs are interchangeable or otherwise universally appropriate to prescribe for an individual in place of Entresto or that these are the only pharmaceutical treatments that might be used by a person with the indication treated by Entresto. CMS trusts that patients and health care providers will continue to choose the therapy that best suits a given patient's needs based on the patient's health, history, experience, and preferences, the provider's expertise, FDA-approved prescribing information, and relevant clinical guidelines, as applicable.

During the negotiation process, CMS identified therapeutic alternatives to Entresto based on a holistic consideration of the available evidence from a range of sources. In addition to the sources listed above, such as data submitted by the Primary Manufacturer and the public and widely accepted clinical guidelines, other examples of data sources used include the following: drug classification systems commonly used in the public and commercial sector for formulary development, indications included in CMS-approved Part D compendia, and drug or drug class reviews.

both observational research and research based on randomized samples, that is methodologically rigorous, appropriately powered (i.e., has sufficient sample size) to answer the primary question of the research, and structured to avoid potential false positive findings due to multiple subgroup analyses.”

¹³ The redacted transcript for this patient-focused listening session is available at the following link: <https://www.cms.gov/files/document/entresto-transcript-110123.pdf>.

¹⁴ See section 1194(e)(2) of the Act and sections 50, 60.3 and 60.4 of the [revised guidance](#) for additional information.

¹⁵ This definition appears in Appendix C of the [revised guidance](#).

The following table lists the therapeutic alternatives, among all clinically comparable alternatives that CMS reviewed, which were particularly relevant to CMS' consideration, due to guideline recommendations, utilization in the Medicare population, and other considerations.

Indication	Therapeutic Alternatives
HF	<ul style="list-style-type: none"> • Enalapril • Lisinopril • Losartan • Spironolactone • Valsartan

Table 2. HF = heart failure. Entresto and its therapeutic alternatives may be differentially used in patients with HF across the spectrum of LVEF function. Use of the term “therapeutic alternative” in this MFP explanation is limited to the purposes and definition outlined in the IRA and the revised guidance. Use of this term does not suggest that CMS believes such drugs are interchangeable or otherwise universally appropriate to prescribe for an individual in place of Entresto or that these are the only pharmaceutical treatments that might be used by a person with the indication treated by Entresto. CMS trusts that patients and health care providers will continue to choose the therapy that best suits a given patient’s needs based on the patient’s health, history, experience, and preferences, the provider’s expertise, FDA-approved prescribing information, and relevant clinical guidelines, as applicable.

Outcomes and Additional Considerations

Outcomes are measurable effects or impacts of a treatment or intervention. Outcomes can be used to measure differences in the safety or effectiveness of different treatments. Patient-centered outcomes are outcomes identified by patients that are important to how they feel, function, or survive. To consider comparative effectiveness between Entresto and therapeutic alternatives to Entresto, CMS identified clinically relevant and patient-centered outcomes of interest from the body of available literature to evaluate for the indication of Entresto. CMS then identified evidence comparing Entresto to therapeutic alternatives based on these outcomes. The following table includes a non-exhaustive list of outcomes that were of interest to CMS in its consideration of Entresto:

Indication	Effectiveness Outcomes	Safety Outcomes
HF	<ul style="list-style-type: none"> • Composite of death from CV causes or hospitalization for HF • Patient-reported health status (e.g., KCCQ) 	<ul style="list-style-type: none"> • Serious adverse events • Tolerability (e.g., discontinuation due to adverse events) • Symptomatic hypotension • Cough • Renal impairment • Hyperkalemia • Angioedema • Gynecomastia • Volume depletion

Table 3. CV = cardiovascular; HF = heart failure; KCCQ = Kansas City Cardiomyopathy Questionnaire. Outcomes identified in this table were of interest to CMS in its evaluation of Entresto. Evidence to support an assessment may not have been available for every outcome of interest.

Outcomes, like those listed above, were identified as being of interest to CMS based on their importance to patients and their ability to measure how effective and safe a drug is when used to treat this indication. For example, death from CV causes and hospitalization for HF are key outcomes that are often used to evaluate effectiveness of treatments for patients with HF. Additionally, HF may impact the lives of patients in many ways. Patient-reported health status, as measured by the Kansas City

Cardiomyopathy Questionnaire, is an important outcome as it assesses heart failure symptoms, such as leg swelling, fatigue, shortness of breath, and the impact of heart failure on a patient's physical and social function, as well as quality of life. The risk of symptomatic hypotension, or low blood pressure that leads to symptoms, and tolerability, or the degree to which patients can tolerate adverse events associated with taking a drug, are outcomes reflecting important safety considerations when evaluating drugs for this indication.

Additionally, CMS considered the extent to which Entresto represents a therapeutic advance as compared to existing therapeutic alternatives, and the extent to which Entresto and its therapeutic alternatives address an unmet medical need. CMS also evaluated access, equity, and health outcomes for specific populations (including individuals with disabilities, the elderly, individuals who are terminally ill, children, and other patient populations).

For the purpose of negotiating the MFP for Entresto, CMS holistically considered the negotiation factors regarding evidence about Entresto and its therapeutic alternatives, including consideration of the clinical benefit of Entresto in the context of its therapeutic alternatives. For example, CMS applied its understanding of the comparative effectiveness of Entresto and its therapeutic alternatives in patients with HF across the spectrum of LVEF function (e.g., enalapril in patients with HFrEF and valsartan in patients with HFpEF), when negotiating with the Primary Manufacturer. CMS' holistic assessment was informed by additional contextual considerations, such as the tolerability of side effects for patients.

Throughout the negotiation process, including the development of the initial offer and in the consideration of any offers and counteroffers, CMS applied these and other factors regarding evidence about Entresto and therapeutic alternatives. The totality of CMS' application of these factors, in conjunction with application of the manufacturer-submitted data negotiation factors described above, informed CMS' negotiation of the MFP with the Primary Manufacturer.

Citations to Data Reviewed during the Negotiation Process for Entresto

CMS provides below a list of citations representative of evidence that CMS reviewed during the negotiation process, including citations provided by the Primary Manufacturer and the public in response to the Negotiation Program information collection request, those included in CMS' initial offer concise justification, and other citations which were considered during the evaluation of the Primary Manufacturer's counteroffer and during negotiation meetings.

Consistent with the IRA and section 1182(e) of Title XI of the Act, CMS did not use evidence from comparative clinical effectiveness research in a manner that treats extending the life of an individual who is elderly, disabled, or terminally ill as of lower value than extending the life of an individual who is younger, nondisabled, or not terminally ill, and, consistent with section 1182(e) of Title XI of the Act, did not use quality adjusted life years (QALYs). Inclusion on this list of a citation that contains such evidence does not mean that CMS used such evidence in the course of the negotiation.

This list is intended to provide insight into the range of evidence that various parties, including CMS and the Primary Manufacturer, identified as being relevant to the negotiation. This list does not represent the totality of evidence that CMS reviewed and considered as part of its holistic consideration of the negotiation factors in the determination of any offers and consideration of any counteroffers.

1. About Heart Failure [Internet]. Georgia: U.S. Centers for Disease Control and Prevention; 2023 Jan 5 [cited 2023 Oct 2]. Available from: https://web.archive.org/web/20231005232118/https://www.cdc.gov/heartdisease/heart_failure.htm.
2. Ahmed A, Allman RM, Fonarow GC, Love TE, Zannad F, Dell'italia LJ, et al. Incident heart failure hospitalization and subsequent mortality in chronic heart failure: a propensity-matched study. *J Card Fail*. 2008;14(3):211-8. doi: 10.1016/j.cardfail.2007.12.001. PubMed PMID: 18381184; PubMed Central PMCID: PMC2771194.
3. Albert NM, Swindle JP, Buysman EK, Chang C. Lower Hospitalization and Healthcare Costs With Sacubitril/Valsartan Versus Angiotensin-Converting Enzyme Inhibitor or Angiotensin-Receptor Blocker in a Retrospective Analysis of Patients With Heart Failure. *J Am Heart Assoc*. 2019;8(9):e011089. doi: 10.1161/JAHA.118.011089. PubMed PMID: 31023122; PubMed Central PMCID: PMC6512093.
4. Allen LA, Stevenson LW, Grady KL, Goldstein NE, Matlock DD, Arnold RM, et al. Decision making in advanced heart failure: a scientific statement from the American Heart Association. *Circulation*. 2012;125(15):1928-52. Epub 20120305. doi: 10.1161/CIR.0b013e31824f2173. PubMed PMID: 22392529; PubMed Central PMCID: PMC3893703.
5. Burke JP, Sahli B, and Gleason PP. Sacubitril-Valsartan Real-World Assessment of Total Cost of Care and Resource Utilization Pre/Post Initiation Among Commercially Insured Members with Reduced Ejection Fraction Heart Failure. *Journal of Managed Care & Specialty Pharmacy*. 2020;26(10-a Suppl):S1-S101. doi: 10.18553/jmcp.2020.26.10-a.s1.
6. Castro Diez C, Khalil F, Schwender H, Dalinghaus M, Jovanovic I, Makowski N, et al. Pharmacotherapeutic management of paediatric heart failure and ACE-I use patterns: a European survey. *BMJ Paediatr Open*. 2019;3(1):e000365. Epub 20190131. doi:

- 10.1136/bmjpo-2018-000365. PubMed PMID: 30815586; PubMed Central PMCID: PMC6361374.
7. Center for Drug Evaluation and Research. Entresto (sacubitril and valsartan). U.S. Food and Drug Administration [2015 Jul]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207620Orig1s000AdminCorres.pdf.
8. Chapman B, Hellkamp A, Thomas L, Albert N, Butler J, Patterson JH, et al. Use Of Sacubitril-valsartan And Associated Outcomes By Race And Ethnicity In Patients With Heart Failure With Reduced Ejection Fraction: Data From Champ-HF. *Journal of Cardiac Failure*. 2022;28(5):S33-S. PubMed PMID: WOS:000788638800084.
9. CMS Office of Minority Health. Heart Failure Disparities in Medicare Fee-For-Service Beneficiaries. Centers for Medicare and Medicaid Services; 2024 Jan. Available from: <https://www.cms.gov/about-cms/agency-information/omh/downloads/data-snapshot-heart-failure.pdf>.
10. Dargad RR, Prajapati MR, Dargad RR, Parekh JD. Sacubitril/valsartan: A novel angiotensin receptor-neprilysin inhibitor. *Indian Heart J*. 2018;70 Suppl 1(Suppl 1):S102-S10. Epub 20180108. doi: 10.1016/j.ihj.2018.01.002. PubMed PMID: 30122239; PubMed Central PMCID: PMC6097164.
11. Das BB. Current State of Pediatric Heart Failure. *Children (Basel)*. 2018;5(7). Epub 20180628. doi: 10.3390/children5070088. PubMed PMID: 29958420; PubMed Central PMCID: PMC6069285.
12. Delivering Promising New Medicines Without Sacrificing Safety and Efficacy [Internet]. U.S Food & Drug Administration; 2019 Aug 27 [cited 2024 Feb 19]. Available from: <https://www.fda.gov/news-events/fda-voices/delivering-promising-new-medicines-without-sacrificing-safety-and-efficacy>.
13. Desai RJ, Paterno E, Vaduganathan M, Mahesri M, Chin K, Levin R, et al. Effectiveness of angiotensin-neprilysin inhibitor treatment versus renin-angiotensin system blockade in older adults with heart failure in clinical care. *Heart*. 2021;107(17):1407-16. Epub 20210604. doi: 10.1136/heartjnl-2021-319405. PubMed PMID: 34088766.
14. Eadie AL, Brunt KR, Herder M. Exploring the Food and Drug Administration's review and approval of Entresto (sacubitril/valsartan). *Pharmacol Res Perspect*. 2021;9(3):e00794. doi: 10.1002/prp2.794. PubMed PMID: 34087050; PubMed Central PMCID: PMC8177063.
15. Exner DV, Dries DL, Domanski MJ, Cohn JN. Lesser response to angiotensin-converting-enzyme inhibitor therapy in black as compared with white patients with left ventricular dysfunction. *N Engl J Med*. 2001;344(18):1351-7. doi: 10.1056/NEJM200105033441802. PubMed PMID: 11333991.
16. Fast Track [Internet]. U.S Food & Drug Administration; 2018 Jan 4 [cited 2024 Feb 20]. Available from: <https://web.archive.org/web/20240218075333/https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/fast-track>.
17. Fonarow GC, Hernandez AF, Solomon SD, Yancy CW. Potential Mortality Reduction With Optimal Implementation of Angiotensin Receptor Neprilysin Inhibitor Therapy in Heart Failure. *JAMA Cardiol*. 2016;1(6):714-7. doi: 10.1001/jamacardio.2016.1724. PubMed PMID: 27437874.

18. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. *JAMA*. 1995;273(18):1450-6. PubMed PMID: 7654275.
19. Gaziano TA, Fonarow GC, Claggett B, Chan WW, Deschaseaux-Voinet C, Turner SJ, et al. Cost-effectiveness Analysis of Sacubitril/Valsartan vs Enalapril in Patients With Heart Failure and Reduced Ejection Fraction. *JAMA Cardiol*. 2016;1(6):666-72. doi: 10.1001/jamacardio.2016.1747. PubMed PMID: 27438344.
20. 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;5(11):1236-44. doi: 10.1001/jamacardio.2020.2822. PubMed PMID: 32785628; PubMed Central PMCID: PMC7675099.
21. Get With The Guidelines® Heart Failure [Internet]. Texas: American Heart Association; 2022 [cited 2023 Oct 2]. Available from: <https://www.heart.org/en/professional/quality-improvement/get-with-the-guidelines/get-with-the-guidelines-heart-failure>.
22. Gheorghiade M, Pang PS. Acute heart failure syndromes. *J Am Coll Cardiol*. 2009;53(7):557-73. doi: 10.1016/j.jacc.2008.10.041. PubMed PMID: 19215829.
23. Greene SJ, Choi S, Lippmann SJ, Mentz RJ, Greiner MA, Hardy NC, et al. Clinical Effectiveness of Sacubitril/Valsartan Among Patients Hospitalized for Heart Failure With Reduced Ejection Fraction. *J Am Heart Assoc*. 2021;10(16):e021459. Epub 20210805. doi: 10.1161/JAHA.121.021459. PubMed PMID: 34350772; PubMed Central PMCID: PMC8475054.
24. Heart Failure Facts & Information [Internet]. Maryland: Heart Failure Society of America [cited 2023 Oct 2]. Available from: <https://hfsa.org/patient-hub/heart-failure-facts-information>.
25. Heart failure projected to increase dramatically, according to new statistics [Internet]. Texas: American Heart Association; 2017 Jan [cited 2023 Oct 2]. Available from: <https://www.heart.org/en/news/2018/07/19/heart-failure-projected-to-increase-dramatically-according-to-new-statistics>.
26. Heidenreich PA, Albert NM, Allen LA, Bluemke DA, Butler J, Fonarow GC, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circ Heart Fail*. 2013;6(3):606-19. Epub 20130424. doi: 10.1161/HHF.0b013e318291329a. PubMed PMID: 23616602; PubMed Central PMCID: PMC3908895.
27. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, 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*. 2022;79(17):e263-e421. Epub 20220401. doi: 10.1016/j.jacc.2021.12.012. PubMed PMID: 35379503.
28. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2022;79(17):1757-80. Epub 20220401. doi: 10.1016/j.jacc.2021.12.011. PubMed PMID: 35379504.

29. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, 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. *Circulation*. 2022;145(18):e895-e1032. Epub 20220401. doi: 10.1161/CIR.0000000000001063. PubMed PMID: 35363499.
30. Heo S, Doering LV, Widener J, Moser DK. Predictors and effect of physical symptom status on health-related quality of life in patients with heart failure. *Am J Crit Care*. 2008;17(2):124-32. PubMed PMID: 18310649.
31. Jackson SL, Tong X, King RJ, Loustalot F, Hong Y, Ritchey MD. National Burden of Heart Failure Events in the United States, 2006 to 2014. *Circ Heart Fail*. 2018;11(12):e004873. doi: 10.1161/CIRCHEARTFAILURE.117.004873. PubMed PMID: 30562099; PubMed Central PMCID: PMC6424109.
32. Jain V, Minhas AMK, Morris AA, Greene SJ, Pandey A, Khan SS, et al. Demographic and Regional Trends of Heart Failure-Related Mortality in Young Adults in the US, 1999-2019. *JAMA Cardiol*. 2022;7(9):900-4. doi: 10.1001/jamacardio.2022.2213. PubMed PMID: 35895048; PubMed Central PMCID: PMC9330269.
33. Januzzi JL, Butler J, Fombu E, Maisel A, McCague K, Pina IL, et al. Rationale and methods of the Prospective Study of Biomarkers, Symptom Improvement, and Ventricular Remodeling During Sacubitril/Valsartan Therapy for Heart Failure (PROVE-HF). *Am Heart J*. 2018;199:130-6. Epub 20180213. doi: 10.1016/j.ahj.2017.12.021. PubMed PMID: 29754651.
34. Kemp CD, Conte JV. The pathophysiology of heart failure. *Cardiovasc Pathol*. 2012;21(5):365-71. Epub 20120105. doi: 10.1016/j.carpath.2011.11.007. PubMed PMID: 22227365.
35. Khariton Y, Fonarow GC, Arnold SV, Hellkamp A, Nassif ME, Sharma PP, et al. Association Between Sacubitril/Valsartan Initiation and Health Status Outcomes in Heart Failure With Reduced Ejection Fraction. *JACC Heart Fail*. 2019;7(11):933-41. Epub 20190911. doi: 10.1016/j.jchf.2019.05.016. PubMed PMID: 31521679; PubMed Central PMCID: PMC7122134.
36. Khera R, Kondamudi N, Zhong L, Vaduganathan M, Parker J, Das SR, et al. Temporal Trends in Heart Failure Incidence Among Medicare Beneficiaries Across Risk Factor Strata, 2011 to 2016. *JAMA Netw Open*. 2020;3(10):e2022190. Epub 20201001. doi: 10.1001/jamanetworkopen.2020.22190. PubMed PMID: 33095250; PubMed Central PMCID: PMC7584929.
37. Kirk R, Dipchand AI, Rosenthal DN, Addonizio L, Burch M, Chrisant M, et al. The International Society for Heart and Lung Transplantation Guidelines for the management of pediatric heart failure: Executive summary. [Corrected]. *J Heart Lung Transplant*. 2014;33(9):888-909. Epub 20140617. doi: 10.1016/j.healun.2014.06.002. PubMed PMID: 25110323.
38. Kittleson MM, Panjrath GS, Amancherla K, Davis LL, Deswal A, Dixon DL, et al. 2023 ACC Expert Consensus Decision Pathway on Management of Heart Failure With Preserved Ejection Fraction: A Report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2023;81(18):1835-78. Epub 20230419. doi: 10.1016/j.jacc.2023.03.393. PubMed PMID: 37137593.
39. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, 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*. 2015;28(1):1-39 e14. doi: 10.1016/j.echo.2014.10.003. PubMed PMID: 25559473.
40. Lesman-Leegte I, Jaarsma T, Coyne JC, Hillege HL, Van Veldhuisen DJ, Sanderman R. Quality of life and depressive symptoms in the elderly: a comparison between patients with heart failure and age- and gender-matched community controls. *J Card Fail*. 2009;15(1):17-23. Epub 20081128. doi: 10.1016/j.cardfail.2008.09.006. PubMed PMID: 19181289.
 41. Lewis EF, Claggett BL, McMurray JJV, Packer M, Lefkowitz MP, Rouleau JL, et al. Health-Related Quality of Life Outcomes in PARADIGM-HF. *Circ Heart Fail*. 2017;10(8). doi: 10.1161/CIRCHEARTFAILURE.116.003430. PubMed PMID: 28784687.
 42. Lumbers RT, Martin N, Manoharan K, Thomas J, Davies LC. Do beta-blockers and inhibitors of the renin-angiotensin aldosterone system improve outcomes in patients with heart failure and left ventricular ejection fraction >40%? *Heart*. 2019;105(20):1533-5. Epub 20190725. doi: 10.1136/heartjnl-2018-313855. PubMed PMID: 31345952.
 43. Maddox TM, Januzzi JL, Jr., Allen LA, Breathett K, Brouse S, Butler J, et al. 2024 ACC Expert Consensus Decision Pathway for Treatment of Heart Failure With Reduced Ejection Fraction: A Report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2024;83(15):1444-88. Epub 20240308. doi: 10.1016/j.jacc.2023.12.024. PubMed PMID: 38466244.
 44. Mangiafico S, Costello-Boerrigter LC, Andersen IA, Cataliotti A, Burnett JC, Jr. Neutral endopeptidase inhibition and the natriuretic peptide system: an evolving strategy in cardiovascular therapeutics. *Eur Heart J*. 2013;34(12):886-93c. Epub 20120831. doi: 10.1093/eurheartj/ehs262. PubMed PMID: 22942338; PubMed Central PMCID: PMC3604644.
 45. Mann DL, Givertz MM, Vader JM, Starling RC, Shah P, McNulty SE, et al. Effect of Treatment With Sacubitril/Valsartan in Patients With Advanced Heart Failure and Reduced Ejection Fraction: A Randomized Clinical Trial. *JAMA Cardiol*. 2022;7(1):17-25. doi: 10.1001/jamacardio.2021.4567. PubMed PMID: 34730769; PubMed Central PMCID: PMC8567189.
 46. Mann DL, Zipes DP, Libby P, Bonow RO. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 10th ed. Elsevier; c2014. Chapter 22, Pathophysiology of Heart Failure.
 47. McKay B. Heart Attack at 49—America's Biggest Killer Makes a Deadly Comeback [Internet]. *The Wall Street Journal*; 2019 Jun 21 [cited 2023 Oct 2]. Available from: <https://www.wsj.com/articles/after-decades-of-progress-america-backslides-on-heart-disease-11561129106>.
 48. McMurray J, Packer M, Desai A, Gong J, Greenlaw N, Lefkowitz M, et al. A putative placebo analysis of the effects of LCZ696 on clinical outcomes in heart failure. *Eur Heart J*. 2015;36(7):434-9. doi: 10.1093/eurheartj/ehu455. PubMed PMID: 25416329; PubMed Central PMCID: PMC4328198.
 49. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure

- Association (HFA) of the ESC. *Eur Heart J*. 2012;33(14):1787-847. Epub 20120519. doi: 10.1093/eurheartj/ehs104. PubMed PMID: 22611136.
50. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz M, Rizkala AR, et al. Baseline characteristics and treatment of patients in prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure trial (PARADIGM-HF). *Eur J Heart Fail*. 2014;16(7):817-25. Epub 20140603. doi: 10.1002/ejhf.115. PubMed PMID: 24828035; PubMed Central PMCID: PMC4312884.
 51. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371(11):993-1004. Epub 20140830. doi: 10.1056/NEJMoa1409077. PubMed PMID: 25176015.
 52. Mentz RJ, Ward JH, Hernandez AF, Lepage S, Morrow DA, Sarwat S, et al. Angiotensin-Neprilysin Inhibition in Patients With Mildly Reduced or Preserved Ejection Fraction and Worsening Heart Failure. *J Am Coll Cardiol*. 2023;82(1):1-12. Epub 20230521. doi: 10.1016/j.jacc.2023.04.019. PubMed PMID: 37212758.
 53. Mentz RJ, Xu HL, O'Brien EC, Thomas L, Alexy T, Gupta B, et al. Provide-Hf Study Results: Patient-Reported Outcomes Investigation Following Initiation of Drug Therapy with Entresto (Sacubitril/Valsartan) in Heart Failure. *Journal of the American College of Cardiology*. 2020;75(11):810-. PubMed PMID: WOS:000522979100796.
 54. Mohanty AF, Levitan EB, Dodson JA, Vardeny O, King JB, LaFleur J, et al. Characteristics and Healthcare Utilization Among Veterans Treated for Heart Failure With Reduced Ejection Fraction Who Switched to Sacubitril/Valsartan. *Circ Heart Fail*. 2019;12(11):e005691. Epub 20191113. doi: 10.1161/CIRCHEARTFAILURE.118.005691. PubMed PMID: 31718321.
 55. Morrow DA, Velazquez EJ, DeVore AD, Desai AS, Duffy CI, Ambrosy AP, et al. Clinical Outcomes in Patients With Acute Decompensated Heart Failure Randomly Assigned to Sacubitril/Valsartan or Enalapril in the PIONEER-HF Trial. *Circulation*. 2019;139(19):2285-8. doi: 10.1161/CIRCULATIONAHA.118.039331. PubMed PMID: 30955360.
 56. Muntwyler J, Abetel G, Gruner C, Follath F. One-year mortality among unselected outpatients with heart failure. *Eur Heart J*. 2002;23(23):1861-6. doi: 10.1053/euhj.2002.3282. PubMed PMID: 12445535.
 57. Nathisuwan S, Talbert RL. A Review of Vasopeptidase Inhibitors: A New Modality in the Treatment of Hypertension and Chronic Heart Failure. *Pharmacotherapy*. 2002;22(1):27-42. doi: 10.1592/phco.22.1.27.33502.
 58. National Center for Health Statistics. National Health and Nutrition Examination Survey [Internet]. U.S. Centers for Disease Control and Prevention; 2024 [cited 2023 Oct 2]. Available from: <https://www.cdc.gov/nchs/nhanes/index.htm>.
 59. Nguyen C, Connolly L, Suminska S, Noone G, Banerjee S, Shen X. Impact of sacubitril/valsartan initiation on all-cause medical costs in commercially insured and Medicare Advantage patients with chronic heart failure: a real-world analysis. *J Manag Care Spec Pharm*. 2022;28(3a Suppl):S55. doi: 10.18553/jmcp.2022.28.3-a.s1.
 60. Novartis Europharm Limited. Entresto (sacubitril and valsartan) [package insert]. European Medicines Agency. Renewed 2020 Jun. Available from: https://www.ema.europa.eu/en/documents/product-information/entresto-epar-product-information_en.pdf.

61. Novartis Pharmaceuticals Corporation. Entresto (sacubitril and valsartan) [package insert]. U.S. Food and Drug Administration. Revised 2019 Oct. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/207620s013lbl.pdf.
62. Novartis Pharmaceuticals Corporation. Entresto (sacubitril and valsartan) [package insert]. U.S. Food and Drug Administration. Revised 2021 Feb. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/207620s018lbl.pdf.
63. Pascual-Figal D, Bayes-Genis A, Beltran-Troncoso P, Caravaca-Perez P, Conde-Martel A, Crespo-Leiro MG, et al. Sacubitril-Valsartan, Clinical Benefits and Related Mechanisms of Action in Heart Failure With Reduced Ejection Fraction. A Review. *Front Cardiovasc Med*. 2021;8:754499. Epub 20211111. doi: 10.3389/fcvm.2021.754499. PubMed PMID: 34859070; PubMed Central PMCID: PMC8631913.
64. Patel J. Heart failure population health considerations. *Am J Manag Care*. 2021;27(9 Suppl):S191-S5. doi: 10.37765/ajmc.2021.88673. PubMed PMID: 34042417.
65. Pierce JB, Blumer V, Choi S, Hardy NC, Greiner MA, Carnicelli AP, et al. Comparative Outcomes of Sacubitril/Valsartan Use After Hospitalization for Heart Failure Among Medicare Beneficiaries Naive to Renin-Angiotensin System Inhibitors. *Am J Cardiol*. 2023;204:151-8. Epub 20230804. doi: 10.1016/j.amjcard.2023.07.099. PubMed PMID: 37544137.
66. Pieske B, Wachter R, Shah SJ, Baldrige A, Szczepoedy P, Ibram G, et al. Effect of Sacubitril/Valsartan vs Standard Medical Therapies on Plasma NT-proBNP Concentration and Submaximal Exercise Capacity in Patients With Heart Failure and Preserved Ejection Fraction: The PARALLAX Randomized Clinical Trial. *JAMA*. 2021;326(19):1919-29. doi: 10.1001/jama.2021.18463. PubMed PMID: 34783839; PubMed Central PMCID: PMC8596197.
67. Pina IL, Camacho A, Ibrahim NE, Felker GM, Butler J, Maisel AS, et al. Improvement of Health Status Following Initiation of Sacubitril/Valsartan in Heart Failure and Reduced Ejection Fraction. *JACC Heart Fail*. 2021;9(1):42-51. Epub 20201111. doi: 10.1016/j.jchf.2020.09.012. PubMed PMID: 33189630.
68. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *European journal of heart failure*. 2016;18(8):891-975. doi: 10.1002/ejhf.592.
69. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016;37(27):2129-200. Epub 20160520. doi: 10.1093/eurheartj/ehw128. PubMed PMID: 27206819.
70. Poster Abstracts - Academy of Managed Care Pharmacy 2022. *Journal of Managed Care & Specialty Pharmacy*. 2022;28(3-a Suppl):S1-S104. doi: 10.18553/jmcp.2022.28.3-a.s1.
71. Proudfoot C, Studer R, Rajput T, Jindal R, Agrawal R, Corda S, et al. Real-world effectiveness and safety of sacubitril/valsartan in heart failure: A systematic review. *Int J Cardiol*. 2021;331:164-71. Epub 20210203. doi: 10.1016/j.ijcard.2021.01.061. PubMed PMID: 33545266.

72. Rodriguez-Artalejo F, Guallar-Castillon P, Pascual CR, Otero CM, Montes AO, Garcia AN, et al. Health-related quality of life as a predictor of hospital readmission and death among patients with heart failure. *Arch Intern Med*. 2005;165(11):1274-9. doi: 10.1001/archinte.165.11.1274. PubMed PMID: 15956007.
73. Sawyer A, Flagg LA. State Declines in Heart Disease Mortality in the United States, 2000–2019. U.S. Centers for Disease Control and Prevention; 2021 Dec. Available from: <https://www.cdc.gov/nchs/data/databriefs/db425.pdf>.
74. Shafrin J, Aliyev ER, Brauer M, Park S, Shen X. Alternative payment models and innovation: a case study of US health system adoption of a sacubitril/valsartan to treat acute decompensated heart failure. *J Med Econ*. 2020;23(12):1450-60. Epub 20201007. doi: 10.1080/13696998.2020.1825454. PubMed PMID: 32945737.
75. Shen X, Schwartz TT, Sullivan G, Adelsberg M, Francis M, Petrilla A, et al. Sacubitril/Valsartan in Medicare Alternative Payment Models. *The American Journal of Accountable Care*. 2023;11(1):5-17. doi: 10.37765/ajac.2023.89339.
76. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, et al. Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. *N Engl J Med*. 2019;381(17):1609-20. Epub 20190901. doi: 10.1056/NEJMoa1908655. PubMed PMID: 31475794.
77. Solomon SD, Vaduganathan M, B LC, Packer M, Zile M, Swedberg K, et al. Sacubitril/Valsartan Across the Spectrum of Ejection Fraction in Heart Failure. *Circulation*. 2020;141(5):352-61. Epub 20191117. doi: 10.1161/CIRCULATIONAHA.119.044586. PubMed PMID: 31736342.
78. Spertus JA, Jones PG, Sandhu AT, Arnold SV. Interpreting the Kansas City Cardiomyopathy Questionnaire in Clinical Trials and Clinical Care: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2020;76(20):2379-90. doi: 10.1016/j.jacc.2020.09.542. PubMed PMID: 33183512.
79. Tan NY, Sangaralingham LR, Sangaralingham SJ, Yao X, Shah ND, Dunlay SM. Comparative Effectiveness of Sacubitril-Valsartan Versus ACE/ARB Therapy in Heart Failure With Reduced Ejection Fraction. *JACC Heart Fail*. 2020;8(1):43-54. Epub 20191211. doi: 10.1016/j.jchf.2019.08.003. PubMed PMID: 31838035; PubMed Central PMCID: PMC8356205.
80. The Impact of Non-Medical Switching on Patients Taking a Blood Thinner. The American Society for Preventive Cardiology; 2022 Aug. Available from: https://assets.noviams.com/novi-file-uploads/aspc/pdfs_and_documents/Advocacy_Statements/ASPC-NMSBloodThinner-SurveyReport-August2022-b33dab04.pdf.
81. Thomas M, Khariton Y, Fonarow GC, Arnold SV, Hill L, Nassif ME, et al. Association between sacubitril/valsartan initiation and real-world health status trajectories over 18 months in heart failure with reduced ejection fraction. *ESC Heart Fail*. 2021;8(4):2670-8. Epub 20210501. doi: 10.1002/ehf2.13298. PubMed PMID: 33932120; PubMed Central PMCID: PMC8318450.
82. Vaduganathan M, Jhund PS, Claggett BL, Packer M, Widimsky J, Seferovic P, et al. A putative placebo analysis of the effects of sacubitril/valsartan in heart failure across the full range of ejection fraction. *Eur Heart J*. 2020;41(25):2356-62. doi: 10.1093/eurheartj/ehaa184. PubMed PMID: 32221596; PubMed Central PMCID: PMC7327532.

83. Valsartan and Sacubitril [Internet]. Maryland: MedlinePlus; 2024 Jul 20 [cited 2023 Oct 2]. Available from: <https://medlineplus.gov/druginfo/meds/a615039.html>.
84. Velazquez EJ, Morrow DA, DeVore AD, Duffy CI, Ambrosy AP, McCague K, et al. Angiotensin-Neprilysin Inhibition in Acute Decompensated Heart Failure. *N Engl J Med*. 2019;380(6):539-48. Epub 20181111. doi: 10.1056/NEJMoa1812851. PubMed PMID: 30415601.
85. Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, et al. Heart Disease and Stroke Statistics-2021 Update: A Report From the American Heart Association. *Circulation*. 2021;143(8):e254-e743. Epub 20210127. doi: 10.1161/CIR.0000000000000950. PubMed PMID: 33501848.
86. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, et al. Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association. *Circulation*. 2020;141(9):e139-e596. Epub 20200129. doi: 10.1161/CIR.0000000000000757. PubMed PMID: 31992061.
87. Wang Y, Zhou R, Lu C, Chen Q, Xu T, Li D. Effects of the Angiotensin-Receptor Neprilysin Inhibitor on Cardiac Reverse Remodeling: Meta-Analysis. *J Am Heart Assoc*. 2019;8(13):e012272. Epub 20190626. doi: 10.1161/JAHA.119.012272. PubMed PMID: 31240976; PubMed Central PMCID: PMC6662364.
88. Writing Committee Members, ACC/AHA Joint Committee Members. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. *J Card Fail*. 2022;28(5):e1-e167. Epub 20220401. doi: 10.1016/j.cardfail.2022.02.010. PubMed PMID: 35378257.
89. Writing Committee Members, Maddox TM, Januzzi JL, Jr., Allen LA, Breathett K, Butler J, et al. 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction: A Report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2021;77(6):772-810. Epub 20210111. doi: 10.1016/j.jacc.2020.11.022. PubMed PMID: 33446410.
90. Writing Committee Members, Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., 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*. 2016;134(13):e282-93. Epub 20160520. doi: 10.1161/CIR.0000000000000435. PubMed PMID: 27208050.
91. Writing Committee Members, Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., 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*. 2013;128(16):e240-327. Epub 20130605. doi: 10.1161/CIR.0b013e31829e8776. PubMed PMID: 23741058.
92. Xiang B, Zhang R, Wu X, Zhou X. Optimal Pharmacologic Treatment of Heart Failure With Preserved and Mildly Reduced Ejection Fraction: A Meta-analysis. *JAMA Netw Open*. 2022;5(9):e2231963. Epub 20220901. doi: 10.1001/jamanetworkopen.2022.31963. PubMed PMID: 36125813; PubMed Central PMCID: PMC9490501.
93. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Colvin MM, 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*. 2017;136(6):e137-e61. Epub 20170428. doi: 10.1161/CIR.0000000000000509. PubMed PMID: 28455343.
94. Ziaeian B, Kominski GF, Ong MK, Mays VM, Brook RH, Fonarow GC. National Differences in Trends for Heart Failure Hospitalizations by Sex and Race/Ethnicity. *Circ Cardiovasc Qual Outcomes*. 2017;10(7). doi: 10.1161/CIRCOUTCOMES.116.003552. PubMed PMID: 28655709; PubMed Central PMCID: PMC5540644.

Redacted Negotiation Meeting Summaries for Entresto

Below are summaries of the negotiation meetings between CMS and the Primary Manufacturer, which include redacted information regarding the negotiation meetings and exchange of offers and counteroffers in the meetings.



SUBJECT: Meeting Summary from Negotiation Meeting between the Centers for Medicare & Medicaid Services (CMS) and Novartis Pharms Corp regarding Entresto on May 3, 2024

Background: Sections 11001 and 11002 of the Inflation Reduction Act of 2022 (IRA) (P.L. 117-169), signed into law on August 16, 2022, established the Medicare Drug Price Negotiation Program (hereafter the “Negotiation Program”) to enable the Centers for Medicare & Medicaid Services (CMS) to negotiate maximum fair prices (MFPs) with willing manufacturers for certain high expenditure, single source drugs and biological products. Novartis Pharms Corp (hereafter “the Primary Manufacturer”) chose to enter into an agreement to participate in the Negotiation Program for Entresto (hereafter “the Selected Drug”).

In accordance with revised guidance and in the course of negotiation for the Selected Drug, CMS invited the Primary Manufacturer to a negotiation meeting when rejecting the Primary Manufacturer’s counteroffer, and the Primary Manufacturer accepted CMS’ invitation. CMS shared a proposed meeting agenda with the Primary Manufacturer approximately two weeks before the meeting. The Primary Manufacturer had the opportunity to request additions or edits to the agenda at least one week ahead of the meeting. This document includes a summary prepared by CMS of the first negotiation meeting, which was held on May 3, 2024 between 12:30 PM ET and 3:00 PM ET.

CMS Attendees:

1. Scott Falin, Representative from the Office of the General Counsel
2. Dan Heider, Director, Division of Rebate Agreements and Drug Price Negotiation
3. Katherine Kehres, Division of Rebate Agreements and Drug Price Negotiation
4. Ji Lee, Division of Rebate Agreements and Drug Price Negotiation
5. Tina Li, Medicare Drug Rebate and Negotiations Group
6. Lara Strawbridge, Deputy Director of Policy, Medicare Drug Rebate and Negotiations Group

Primary Manufacturer Attendees:

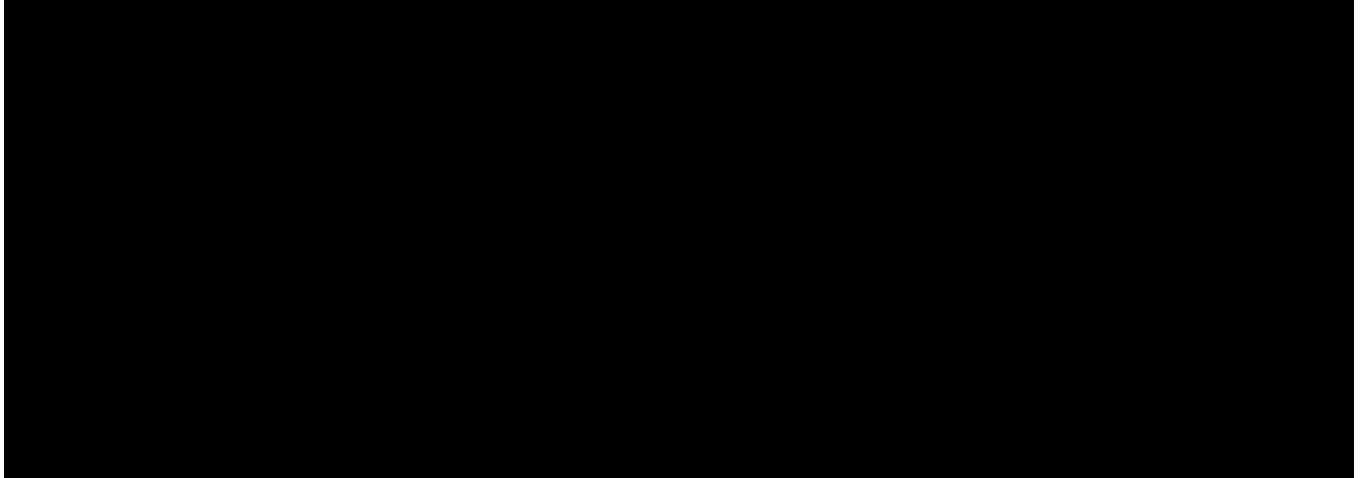
1. Dan DiMeo, Executive Director, Pricing and Account Management
2. Alexis Meyers, Head, Market Access Legal (virtual attendance)
3. Lisa Nelson, Head, US Public Policy
4. Courtney Piron, Head, US Public Affairs
5. Rob Rubinsky, Chief Market Access Officer
6. Kristin Williamson, Executive Director, US Medical

Topics: The discussion focused on topics outlined in the final agenda for the meeting, which was as follows:¹

- Introductions and meeting reminders
- Discussion of initial offer and any questions from the Primary Manufacturer
- Discussion of counteroffer and any questions from CMS
- Any other considerations that CMS and the Primary Manufacturer would like to discuss
- Next steps

¹ Note: This agenda may be inclusive of topics proposed by the Primary Manufacturer.

Offers/Counteroffers Exchanged:





SUBJECT: Meeting Summary from Negotiation Meeting between the Centers for Medicare & Medicaid Services (CMS) and Novartis Pharms Corp regarding Entresto on May 21, 2024

Background: Sections 11001 and 11002 of the Inflation Reduction Act of 2022 (IRA) (P.L. 117-169), signed into law on August 16, 2022, established the Medicare Drug Price Negotiation Program (hereafter the “Negotiation Program”) to enable the Centers for Medicare & Medicaid Services (CMS) to negotiate maximum fair prices (MFPs) with willing manufacturers for certain high expenditure, single source drugs and biological products. Novartis Pharms Corp (hereafter “the Primary Manufacturer”) chose to enter into an agreement to participate in the Negotiation Program for Entresto (hereafter “the Selected Drug”).

In accordance with revised guidance and in the course of negotiation for the Selected Drug, because CMS and the Primary Manufacturer did not reach agreement on an MFP in the first negotiation meeting held on May 3, 2024, each party had the opportunity to request one additional negotiation meeting, resulting in a maximum of three meetings. CMS requested a second negotiation meeting and the Primary Manufacturer accepted the invitation. CMS shared a proposed meeting agenda with the Primary Manufacturer approximately two weeks before the meeting. The Primary Manufacturer had the opportunity to request additions or edits to the agenda at least one week ahead of the meeting. This document includes a summary prepared by CMS of the second negotiation meeting, which was held on May 21, 2024 between 1:30 PM ET and 4:00 PM ET.

CMS Attendees:

1. Martin Calabrese, Division of Rebate Agreements and Drug Price Negotiation
2. Scott Falin, Representative from the Office of the General Counsel
3. Dan Heider, Director, Division of Rebate Agreements and Drug Price Negotiation
4. Tina Li, Medicare Drug Rebate and Negotiations Group
5. Corey Rosenberg, Deputy Director, Division of Rebate Agreements and Drug Price Negotiation
6. Lara Strawbridge, Deputy Director of Policy, Medicare Drug Rebate and Negotiations Group

Primary Manufacturer Attendees:

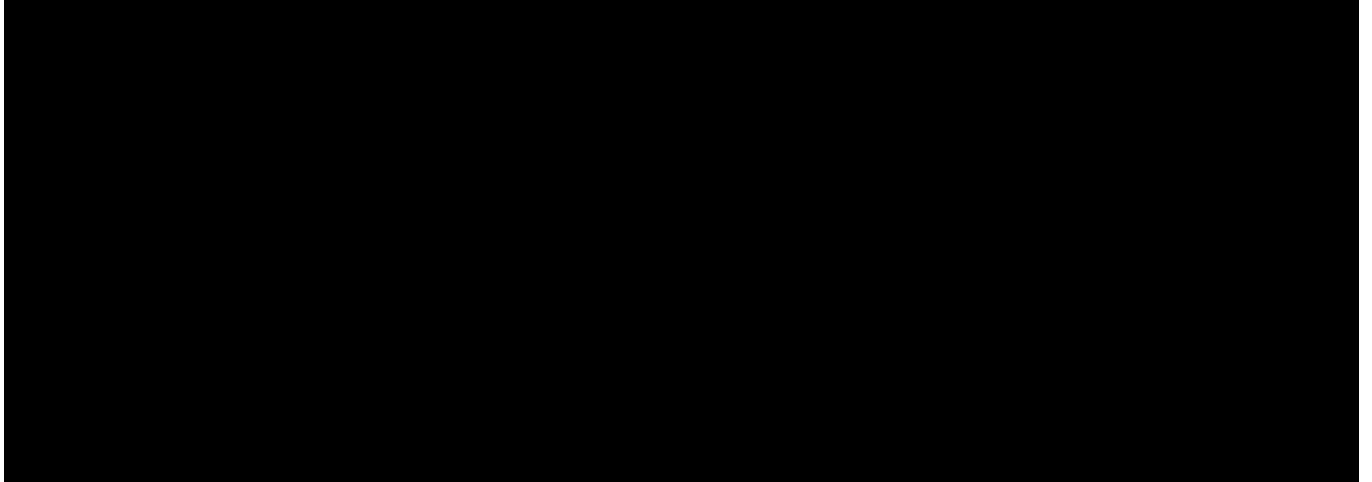
1. Dan DiMeo, Head, Pricing and Access, Entresto
2. Alexis Meyers, Vice President, Market Access Legal (virtual attendance)
3. Lisa Nelson, Head, US Public Policy
4. Courtney Piron, Head, US Public Affairs
5. Rob Rubinsky, Chief Market Access Officer
6. Xian Shen, Pricing and Access

Topics: The discussion focused on topics outlined in the final agenda for the meeting, which was as follows:¹

- Introductions and meeting reminders
- Discussion of Entresto utilization trends across heart failure subpopulations
- Any additional information from Primary Manufacturer on medical cost offset data
- Any additional information from Primary Manufacturer on the impact of previously discussed access concerns
- Any other considerations that CMS or the Primary Manufacturer would like to discuss
- Next steps

¹ Note: This agenda may be inclusive of topics proposed by the Primary Manufacturer.

Offers/Counteroffers Exchanged:





SUBJECT: Meeting Summary from Negotiation Meeting between the Centers for Medicare & Medicaid Services (CMS) and Novartis Pharms Corp regarding Entresto on June 18, 2024

Background: Sections 11001 and 11002 of the Inflation Reduction Act of 2022 (IRA) (P.L. 117-169), signed into law on August 16, 2022, established the Medicare Drug Price Negotiation Program (hereafter the “Negotiation Program”) to enable the Centers for Medicare & Medicaid Services (CMS) to negotiate maximum fair prices (MFPs) with willing manufacturers for certain high expenditure, single source drugs and biological products. Novartis Pharms Corp (hereafter “the Primary Manufacturer”) chose to enter into an agreement to participate in the Negotiation Program for Entresto (hereafter “the Selected Drug”).

In accordance with revised guidance and in the course of negotiation for the Selected Drug, because CMS and the Primary Manufacturer did not reach agreement on an MFP in the second negotiation meeting which was requested by CMS and held on May 21, 2024, the Primary Manufacturer had the opportunity to request one additional negotiation meeting, resulting in a maximum of three meetings. The Primary Manufacturer requested a third negotiation meeting and CMS accepted the invitation. CMS shared a proposed meeting agenda with the Primary Manufacturer approximately two weeks before the meeting. The Primary Manufacturer had the opportunity to request additions or edits to the agenda at least one week ahead of the meeting. This document includes a summary prepared by CMS of the third negotiation meeting, which was held on June 18, 2024 between 1:30 PM ET and 4:00 PM ET.

CMS Attendees:

1. Scott Falin, Representative from the Office of the General Counsel (virtual attendance)
2. Dan Heider, Director, Division of Rebate Agreements and Drug Price Negotiation
3. Ji Lee, Division of Rebate Agreements and Drug Price Negotiation
4. Tina Li, Medicare Drug Rebate and Negotiations Group
5. Corey Rosenberg, Deputy Director, Division of Rebate Agreements and Drug Price Negotiation
6. Lara Strawbridge, Deputy Director of Policy, Medicare Drug Rebate and Negotiations Group

Primary Manufacturer Attendees:

1. Dan DiMeo, representing Novartis Pharms Corp
2. Alexis Meyers, representing Novartis Pharms Corp (virtual attendance)
3. Lisa Nelson, representing Novartis Pharms Corp
4. Courtney Piron, representing Novartis Pharms Corp
5. Rob Rubinsky, representing Novartis Pharms Corp

Topics: The discussion focused on topics outlined in the final agenda for the meeting, which was as follows:¹

- Introductions and meeting reminders
- Revised offer/counteroffer price discussion
- Any other considerations that CMS and the Primary Manufacturer would like to discuss
- Next steps

¹ Note: This agenda may be inclusive of topics proposed by the Primary Manufacturer.

Offers/Counteroffers Exchanged:

