

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

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.¹ 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.

¹ 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 and described in section 50 of revised guidance.

Section 1194(e)(1) Data Factors

IPAY Year: 2026

Manufacturer: Immunex Corporation

Drug: Enbrel (Etanercept)

Background: 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 & 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:

- C: Research and Development Costs and Recoupment,
- D: Current Unit Costs of Production and Distribution,
- E: Prior Federal Financial Support,
- F: Patents, Exclusivities, and Approvals, and
- G: Market Data and Revenue and Sales Volume Data.

The Primary Manufacturer is responsible for aggregating and reporting all necessary data on its selected drug(s) from other parties, as applicable.

Disclaimers: 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.

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							
<p>Description: 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.</p>							
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

[Redacted content]

[Redacted]

Explanation of Basic Pre-Clinical Research Costs

[Redacted]

Explanation of Post-IND Costs

[Redacted]

[Redacted]

[Redacted]

Explanation of Costs on Allowable

[Redacted]

[Redacted]

Explanation of Costs of Other R&D

[Redacted]

[Redacted]

[REDACTED]

[REDACTED]

Explanation of Global

[REDACTED]

Explanation of U.S. Lifetime Net Revenue

[REDACTED]

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 Production Cost	Average Per Unit Distribution Costs	Indicate Unit Used	Total Unit Volume
58406-0055-04	[REDACTED]	[REDACTED]	ML	[REDACTED]
58406-0044-04	[REDACTED]	[REDACTED]	ML	[REDACTED]
58406-0032-04	[REDACTED]	[REDACTED]	ML	[REDACTED]
58406-0010-04	[REDACTED]	[REDACTED]	ML	[REDACTED]
58406-0021-04	[REDACTED]	[REDACTED]	ML	[REDACTED]

Explanations: Unit Production Costs

[REDACTED]

[Redacted]

Distribution Costs

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

E. Federal Financial Support

Description: 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
		OTH		To the best of our knowledge, Immunex Corporation has not received any Federal financial support for Enbrel.

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
8,063,182	1995-05-19	2028-11-22	N	Y	N	N	UTL	N
8,163,522	1995-05-19	2029-04-24	N	Y	N	N	UTL	N
7,915,225	2009-02-27	2019-08-13	N	N	Y	N	UTL	N

F. Patents, Exclusivities, and Approvals

Patents (Expired and Non-Expired) and Patent Applications

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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
8,119,605	2011-02-04	2019-08-13	N	N	Y	N	UTL	N
8,722,631	2013-02-21	2019-08-13	N	N	Y	N	UTL	N
10,307,483	2018-04-20	2037-10-19	Y	N	N	N	UTL	N
11,491,223	2018-09-27	2037-10-19	Y	N	N	N	UTL	N
11,576,856	2019-04-02	2039-06-22	Y	N	N	N	UTL	N
6,872,549	2003-03-27	2023-05-14	N	Y	N	N	UTL	N
6,924,124	2002-08-23	2022-08-23	N	Y	N	N	UTL	N
7,122,641	2002-12-20	2024-09-28	N	Y	N	N	UTL	N
7,157,557	2002-02-22	2022-10-01	N	Y	N	N	UTL	N
11,192,919	2018-07-23	2035-11-13	N	Y	N	N	UTL	N
7,300,773	2005-08-25	2025-12-22	N	Y	N	N	UTL	N
9,012,180	2008-02-29	2031-05-20	N	Y	N	N	UTL	N
9,988,662	2008-04-22	2031-07-29	N	Y	N	N	UTL	N
10,092,706	2012-04-20	2033-12-05	Y	N	N	N	UTL	N
10,492,990	2014-03-14	2035-07-01	Y	N	N	N	UTL	N
D808,010	2015-12-14	2033-01-16	N	N	N	N	DES	N
D829,890	2017-10-30	2033-10-02	N	N	N	N	DES	N
D819,201	2015-12-14	2033-05-29	N	N	N	N	DES	N
D898908	2018-04-30	2035-10-13	N	N	N	N	DES	N

Explanations: Question 12 lists patents, both expired and unexpired, that Immunex Corporation has asserted against biosimilar etanercept makers and unexpired patents that could reasonably be asserted as of September 1, 2023. Expired patents that were not asserted are not listed as we are not aware of potentially infringing activity that would have allowed us to reasonably assert them as of September 1, 2023. Relevant design patents are also provided.

Patents that Immunex Corporation has asserted against biosimilar etanercept makers

8,063,182 and 8,163,522 (both still in force)

-Patents covering etanercept molecule (active ingredient of Enbrel), compositions comprising etanercept, DNA encoding etanercept, processes for making etanercept

-Assigned to Hoffman La Roche (Roche), rights licensed to Immunex Corporation in 1998

-Filed under pre-GATT patent regime so expire 17 years from date of issuance

-Validity of both patents challenged and upheld in district court litigation, affirmed on appeal. Supreme Court denied Sandoz's petition for Certiorari. *Immunex Corp. v. Sandoz Inc.*, 395 F. Supp. 3d. 366, 421 (D.N.J. 2019); *Immunex Corp. v. Sandoz Inc.*, No 20-1037 (Fed. Cir. 2020); *Immunex Corp. v. Sandoz Inc.*, 964 F.3d 1049 (Fed. Cir. 2020), cert. denied, *Sandoz Inc. v. Immunex Corp.*, 141 S. Ct. 2623 (Mem) (2021)

-Would be asserted again against any other biosimilar etanercept before they expire in 2029

7,915,225; 8,119,605 and 8,722,631 (all expired)

-Covered methods of using etanercept to treat psoriasis, psoriatic arthritis, plaque psoriasis

-Assigned to Immunex Corporation

-Were asserted in litigation against Sandoz and Samsung Bioepis

6,872,549; 6,924,124 and 7,157,557(all expired)

-Covered methods of manufacturing etanercept

-Assigned to Immunex Corporation

-Were asserted in litigation against Samsung Bioepis

Other patents that could reasonably be asserted as of September 1, 2023

10,307,483 and 11,491,223

-Cover buffer-free pharmaceutical formulations of etanercept

-Assigned to Amgen Inc.

-May be designed around (e.g., Sandoz's biosimilar etanercept, Erelzi, contains a buffer)

11,576,856

-Covers methods of formulating etanercept

-Assigned to Amgen Inc.

-May be designed around

7,122,641 and 11,192,919

-Covers methods of manufacturing etanercept

-Assigned to Amgen Inc.

-May be designed around

7,300,773; 9,012,180 and 9,988,662

-Covers methods of manufacturing etanercept

-Assigned to Wyeth

-May be designed around

10,092,706 and 10,492,990

-Covers components of certain Enbrel-containing devices

-Assigned to Amgen Inc.

-May be designed around

D808,010, D829,890, D819,201, and D898,908

-Design patents

-Assigned to Amgen Inc.

-May be designed around

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
ODE	2006-05-27	103795	58406-0010, 58406-0021, 58406-0032, 58406-0044, 58406-0055, 58406-0425, 58406-0435, 58406-0445, 58406-0446, 58406-0455, 58406-0456	Enbrel received orphan drug designation for juvenile rheumatoid arthritis on October 27, 1998. Orphan drug exclusivity for this indication started on May 27, 1999 and ended on May 27, 2006.

Explanations: Enbrel received orphan drug designation for juvenile rheumatoid arthritis on October 27, 1998. Orphan drug exclusivity for this indication started on May 27, 1999 and ended on May 27, 2006.

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
103795	BLA		1998-11-02	Reduction in signs and symptoms of moderately to severely active rheumatoid arthritis in patients who have had an inadequate response to one or more disease-modifying antirheumatic drugs (DMARDs). Etanercept can be used in combination with methotrexate in patients who do not respond adequately to methotrexate alone.	Lyophilized powder 25 mg Link to USPI on FDA website https://www.accessdata.fda.gov/drugsatfda_docs/label/1998/etanimm110298lb.pdf	Immunex Corporation	APP	Original approval
103795	BLA		1999-05-27	Polyarticular course juvenile rheumatoid arthritis (JR4).	Lyophilized powder 0.4 mg/kg (up to a	Immunex Corporation	APP	

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Application (NDA / BLA) Number	Application Type (NDA; BLA)	Class Code	Approval Date	Indication	Dosage Form and Strength	Sponsor	Application Status	Comments
					maximum of 25 mg per dose)			
103795	BLA		2002-01-15	Reducing signs and symptoms of active arthritis in patients with psoriatic arthritis (PsA). Etanercept can be used in combination with methotrexate in patients who do not respond adequately to methotrexate alone.	Lyophilized powder 25 mg Link to USPI on FDA website: https://www.accessdata.fda.gov/drugsatfda_docs/label/2002/etanimm011502L B.pdf	Immunex Corporation	APP	
103795	BLA		2002-09-12	No change	No change	Immunex Corporation	APP	Revise the Clinical Studies and Adverse Reactions sections of the package insert to reflect three-year safety and efficacy

F. Patents, Exclusivities, and Approvals

All Active and Pending FDA Applications and Approvals

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Application (NDA / BLA) Number	Application Type (NDA; BLA)	Class Code	Approval Date	Indication	Dosage Form and Strength	Sponsor	Application Status	Comments
								information in rheumatoid arthritis patients
103795	BLA		2003-07-24	Expand the rheumatoid arthritis indication to include improving physical function.	Lyophilized powder 25 mg	Immunex Corporation	APP	
103795	BLA		2003-07-24	Reducing signs and symptoms in patients with active ankylosing spondylitis	Lyophilized powder 25 mg	Immunex Corporation	APP	
103795	BLA		2003-08-21	Expand the indication to include inhibiting the progression of structural damage of active arthritis in patients with psoriatic arthritis	Lyophilized powder 25 mg	Immunex Corporation	APP	
103795	BLA		2003-10-17		Lyophilized powder 25 or 50 mg	Immunex Corporation	APP	Included a 50 mg once weekly dosing regimen

F. Patents, Exclusivities, and Approvals

All Active and Pending FDA Applications and Approvals

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Application (NDA / BLA) Number	Application Type (NDA; BLA)	Class Code	Approval Date	Indication	Dosage Form and Strength	Sponsor	Application Status	Comments
								for adult rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis patients and juvenile rheumatoid arthritis patients
103795	BLA		2003-11-25		Lyophilized powder 25 mg or 50 mg	Immunex Corporation	APP	Revise the Clinical Studies section of the package insert to include four-year radiographic data for rheumatoid arthritis patients
103795	BLA		2004-04-30	Treatment of adult patients (18 years or older) with chronic	Lyophilized powder 25 or 50 mg	Immunex Corporation	APP	

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
				moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy				
103795	BLA		2004-09-24	Indicated for reducing signs and symptoms, inducing major clinical response inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis. ENBREL CI can be initiated in combination with methotrexate (MTX) or used alone	Lyophilized powder 25 mg	Immunex Corporation	APP	Expanded indication language regarding using with or without concomitant methotrexate

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
103795	BLA		2004-09-27		Lyophilized powder Solution for injection 25 mg or 50 mg	Immunex Corporation	APP	New formulation and presentation of drug product (DP) 50 mg/mL liquid supplied in a single dose pre-filled syringe (PFS)
103795	BLA		2005-05-27	Indicated for reducing signs and symptoms, inhibiting the progression of structural damage of active arthritis, and improving physical function in patients with psoriatic arthritis. ENBREL can be used in combination with methotrexate in patients who do not	Lyophilized powder Solution for injection 25 mg or 50 mg	Immunex Corporation	APP	Revise indications and usage section and clinical studies sections of the package insert based on two year follow-up efficacy, safety, radiographic and physical function data in PsA

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
				respond adequately to methotrexate alone				
103795	BLA		2007-02-01		Lyophilized powder Solution for injection 25 mg or 50 mg	Immunex Corporation	APP	New presentation of etanercept drug product: 25 mg of etanercept supplied in a single-dose prefilled syringe (PFS)
103795	BLA		2015-03-25	Indicated for reducing signs and symptoms, inhibiting the progression of structural damage of active arthritis, and improving physical function in patients with psoriatic arthritis (PsA). Enbrel can be	Lyophilized powder Solution for injection 25 mg or 50 mg	Immunex Corporation	APP	Update the psoriatic arthritis indication statement that Enbrel can be used with or without methotrexate

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.

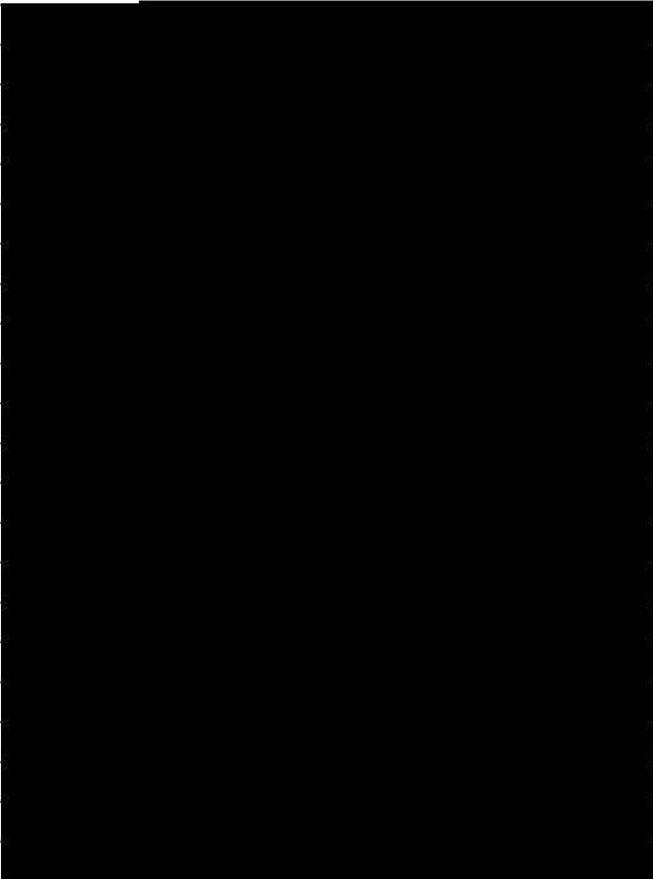
Application (NDA / BLA) Number	Application Type (NDA; BLA)	Class Code	Approval Date	Indication	Dosage Form and Strength	Sponsor	Application Status	Comments
				used with or without methotrexate				
103795	BLA		2016-11-04	Indicated for the treatment of patients 4 years or older with chronic moderate to severe plaque psoriasis (PsO) who are candidates for systemic therapy or phototherapy	Lyophilized powder Solution for injection 25 mg or 50 mg	Immunex Corporation	APP	Pediatric indication added for PsO
103795	BLA		9999-12-31			Immunex Corporation	PEN	Application submitted on December 20, 2022 to add pediatric indication for JPsA

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
58406-0010-04	2018-Q3		ML	
58406-0010-04	2018-Q4		ML	
58406-0010-04	2019-Q1		ML	
58406-0010-04	2019-Q2		ML	
58406-0010-04	2019-Q3	\$ 1,293.52	ML	
58406-0010-04	2019-Q4	\$ 1,293.52	ML	
58406-0010-04	2020-Q1	\$ 1,389.24	ML	
58406-0010-04	2020-Q2	\$ 1,389.24	ML	
58406-0010-04	2020-Q3	\$ 1,389.24	ML	
58406-0010-04	2020-Q4	\$ 1,389.24	ML	
58406-0010-04	2021-Q1	\$ 1,492.04	ML	
58406-0010-04	2021-Q2	\$ 1,492.04	ML	
58406-0010-04	2021-Q3	\$ 1,492.04	ML	
58406-0010-04	2021-Q4	\$ 1,492.04	ML	
58406-0010-04	2022-Q1	\$ 1,602.46	ML	
58406-0010-04	2022-Q2	\$ 1,602.46	ML	
58406-0010-04	2022-Q3	\$ 1,640.92	ML	
58406-0010-04	2022-Q4	\$ 1,640.92	ML	
58406-0010-04	2023-Q1	\$ 1,762.34	ML	
58406-0010-04	2023-Q2	\$ 1,762.34	ML	
58406-0021-04	2018-Q3		ML	
58406-0021-04	2018-Q4		ML	

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
58406-0021-04	2019-Q1		ML	
58406-0021-04	2019-Q2		ML	
58406-0021-04	2019-Q3	\$ 1,293.52	ML	
58406-0021-04	2019-Q4	\$ 1,293.52	ML	
58406-0021-04	2020-Q1	\$ 1,389.24	ML	
58406-0021-04	2020-Q2	\$ 1,389.24	ML	
58406-0021-04	2020-Q3	\$ 1,389.24	ML	
58406-0021-04	2020-Q4	\$ 1,389.24	ML	
58406-0021-04	2021-Q1	\$ 1,492.04	ML	
58406-0021-04	2021-Q2	\$ 1,492.04	ML	
58406-0021-04	2021-Q3	\$ 1,492.04	ML	
58406-0021-04	2021-Q4	\$ 1,492.04	ML	
58406-0021-04	2022-Q1	\$ 1,602.45	ML	
58406-0021-04	2022-Q2	\$ 1,602.45	ML	
58406-0021-04	2022-Q3	\$ 1,640.91	ML	
58406-0021-04	2022-Q4	\$ 1,640.91	ML	
58406-0021-04	2023-Q1	\$ 1,762.34	ML	
58406-0021-04	2023-Q2	\$ 1,762.34	ML	
58406-0032-04	2018-Q3		ML	
58406-0032-04	2018-Q4		ML	
58406-0032-04	2019-Q1		ML	
58406-0032-04	2019-Q2		ML	

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
58406-0032-04	2019-Q3	\$ 1,293.52	ML	
58406-0032-04	2019-Q4	\$ 1,293.52	ML	
58406-0032-04	2020-Q1	\$ 1,389.24	ML	
58406-0032-04	2020-Q2	\$ 1,389.24	ML	
58406-0032-04	2020-Q3	\$ 1,389.24	ML	
58406-0032-04	2020-Q4	\$ 1,389.24	ML	
58406-0032-04	2021-Q1	\$ 1,492.04	ML	
58406-0032-04	2021-Q2	\$ 1,492.04	ML	
58406-0032-04	2021-Q3	\$ 1,492.04	ML	
58406-0032-04	2021-Q4	\$ 1,492.04	ML	
58406-0032-04	2022-Q1	\$ 1,602.45	ML	
58406-0032-04	2022-Q2	\$ 1,602.45	ML	
58406-0032-04	2022-Q3	\$ 1,640.91	ML	
58406-0032-04	2022-Q4	\$ 1,640.91	ML	
58406-0032-04	2023-Q1	\$ 1,762.34	ML	
58406-0032-04	2023-Q2	\$ 1,762.34	ML	
58406-0044-04	2018-Q3		ML	
58406-0044-04	2018-Q4		ML	
58406-0044-04	2019-Q1		ML	
58406-0044-04	2019-Q2		ML	
58406-0044-04	2019-Q3		ML	
58406-0044-04	2019-Q4	\$ 1,293.52	ML	

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
58406-0044-04	2020-Q1	\$ 1,389.24	ML	
58406-0044-04	2020-Q2	\$ 1,389.24	ML	
58406-0044-04	2020-Q3	\$ 1,389.24	ML	
58406-0044-04	2020-Q4	\$ 1,389.24	ML	
58406-0044-04	2021-Q1	\$ 1,492.04	ML	
58406-0044-04	2021-Q2	\$ 1,492.04	ML	
58406-0044-04	2021-Q3	\$ 1,492.04	ML	
58406-0044-04	2021-Q4	\$ 1,492.04	ML	
58406-0044-04	2022-Q1	\$ 1,602.45	ML	
58406-0044-04	2022-Q2	\$ 1,602.45	ML	
58406-0044-04	2022-Q3	\$ 1,640.91	ML	
58406-0044-04	2022-Q4	\$ 1,640.91	ML	
58406-0044-04	2023-Q1	\$ 1,762.34	ML	
58406-0044-04	2023-Q2	\$ 1,762.34	ML	
58406-0055-04	2018-Q3		ML	
58406-0055-04	2018-Q4		ML	
58406-0055-04	2019-Q1		ML	
58406-0055-04	2019-Q2		ML	
58406-0055-04	2019-Q3		ML	
58406-0055-04	2019-Q4		ML	
58406-0055-04	2020-Q1		ML	
58406-0055-04	2020-Q2		ML	

G. Market Data and Revenue and Sales Volume Data

Wholesale Acquisition Cost Unit Price

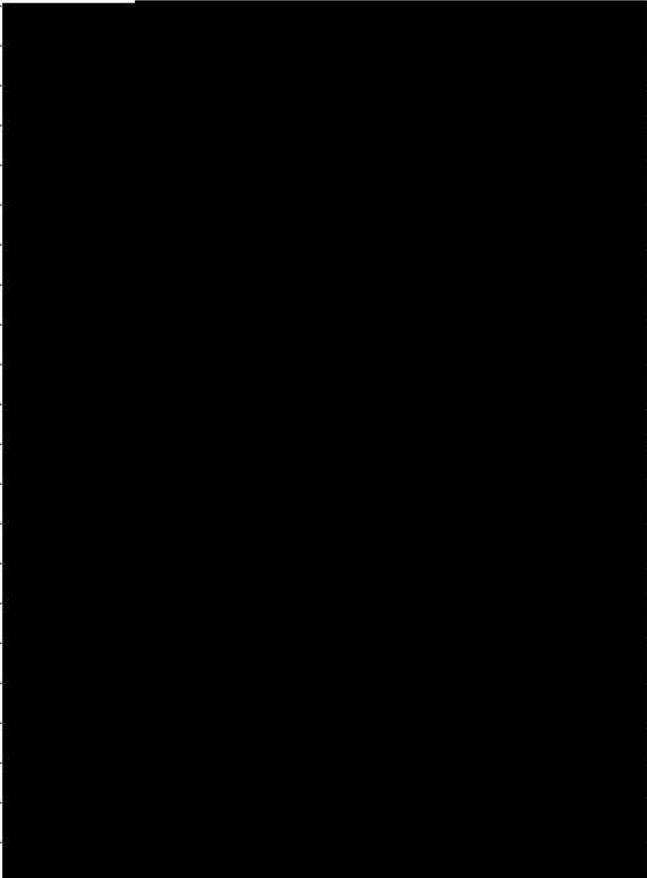
Description: The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Wholesale Acquisition Cost (WAC) unit price of the selected drug.

National Drug Code (NDC-11)	Quarter	WAC	Unit type (each, ML, GM)	Total Unit Volume
58406-0055-04	2020-Q3		ML	[REDACTED]
58406-0055-04	2020-Q4		ML	
58406-0055-04	2021-Q1		ML	
58406-0055-04	2021-Q2		ML	
58406-0055-04	2021-Q3	\$ 1,492.04	ML	
58406-0055-04	2021-Q4	\$ 1,492.04	ML	
58406-0055-04	2022-Q1	\$ 1,602.46	ML	
58406-0055-04	2022-Q2	\$ 1,602.46	ML	
58406-0055-04	2022-Q3	\$ 1,640.92	ML	
58406-0055-04	2022-Q4	\$ 1,640.92	ML	
58406-0055-04	2023-Q1	\$ 1,762.34	ML	
58406-0055-04	2023-Q2	\$ 1,762.34	ML	
58406-0425-34	2018-Q3	\$ 609.00	EA	
58406-0425-34	2018-Q4	\$ 609.00	EA	
58406-0425-34	2019-Q1	\$ 646.76	EA	
58406-0425-34	2019-Q2	\$ 646.76	EA	
58406-0425-34	2019-Q3	\$ 646.76	EA	
58406-0425-34	2019-Q4	\$ 646.76	EA	
58406-0425-34	2020-Q1	\$ 694.62	EA	
58406-0425-34	2020-Q2	\$ 694.62	EA	
58406-0425-34	2020-Q3	\$ 694.62	EA	
58406-0425-34	2020-Q4	\$ 694.62	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
58406-0425-34	2021-Q1	\$ 746.02	EA	
58406-0425-34	2021-Q2	\$ 746.02	EA	
58406-0425-34	2021-Q3	\$ 746.02	EA	
58406-0425-34	2021-Q4	\$ 746.02	EA	
58406-0425-34	2022-Q1	\$ 801.23	EA	
58406-0425-34	2022-Q2	\$ 801.23	EA	
58406-0425-34	2022-Q3		EA	
58406-0425-34	2022-Q4		EA	
58406-0425-34	2023-Q1		EA	
58406-0425-34	2023-Q2		EA	
58406-0435-04	2018-Q3	\$ 1,242.86	ML	
58406-0435-04	2018-Q4	\$ 1,242.86	ML	
58406-0435-04	2019-Q1	\$ 1,319.92	ML	
58406-0435-04	2019-Q2	\$ 1,319.92	ML	
58406-0435-04	2019-Q3	\$ 1,319.92	ML	
58406-0435-04	2019-Q4		ML	
58406-0435-04	2020-Q1		ML	
58406-0435-04	2020-Q2		ML	
58406-0435-04	2020-Q3		ML	
58406-0435-04	2020-Q4		ML	
58406-0435-04	2021-Q1		ML	
58406-0435-04	2021-Q2		ML	

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
58406-0435-04	2021-Q3		ML	
58406-0435-04	2021-Q4		ML	
58406-0435-04	2022-Q1		ML	
58406-0435-04	2022-Q2		ML	
58406-0435-04	2022-Q3		ML	
58406-0435-04	2022-Q4		ML	
58406-0435-04	2023-Q1		ML	
58406-0435-04	2023-Q2		ML	
58406-0445-04	2018-Q3	\$ 1,242.86	ML	
58406-0445-04	2018-Q4	\$ 1,242.86	ML	
58406-0445-04	2019-Q1	\$ 1,319.92	ML	
58406-0445-04	2019-Q2	\$ 1,319.92	ML	
58406-0445-04	2019-Q3	\$ 1,319.92	ML	
58406-0445-04	2019-Q4		ML	
58406-0445-04	2020-Q1		ML	
58406-0445-04	2020-Q2		ML	
58406-0445-04	2020-Q3		ML	
58406-0445-04	2020-Q4		ML	
58406-0445-04	2021-Q1		ML	
58406-0445-04	2021-Q2		ML	
58406-0445-04	2021-Q3		ML	
58406-0445-04	2021-Q4		ML	

G. Market Data and Revenue and Sales Volume Data

Wholesale Acquisition Cost Unit Price

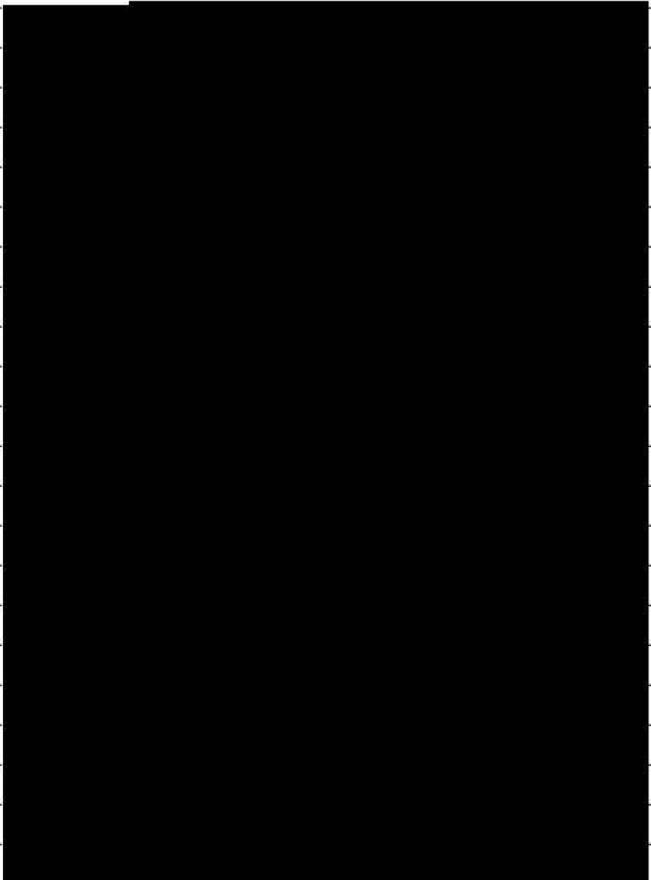
Description: The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Wholesale Acquisition Cost (WAC) unit price of the selected drug.

National Drug Code (NDC-11)	Quarter	WAC	Unit type (each, ML, GM)	Total Unit Volume
58406-0445-04	2022-Q1		ML	
58406-0445-04	2022-Q2		ML	
58406-0445-04	2022-Q3		ML	
58406-0445-04	2022-Q4		ML	
58406-0445-04	2023-Q1		ML	
58406-0445-04	2023-Q2		ML	
58406-0455-04	2018-Q3	\$ 2,388.24	ML	
58406-0455-04	2018-Q4	\$ 2,388.24	ML	
58406-0455-04	2019-Q1	\$ 2,536.31	ML	
58406-0455-04	2019-Q2	\$ 2,536.31	ML	
58406-0455-04	2019-Q3	\$ 2,536.31	ML	
58406-0455-04	2019-Q4		ML	
58406-0455-04	2020-Q1		ML	
58406-0455-04	2020-Q2		ML	
58406-0455-04	2020-Q3		ML	
58406-0455-04	2020-Q4		ML	
58406-0455-04	2021-Q1		ML	
58406-0455-04	2021-Q2		ML	
58406-0455-04	2021-Q3		ML	
58406-0455-04	2021-Q4		ML	
58406-0455-04	2022-Q1		ML	
58406-0455-04	2022-Q2		ML	

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
58406-0455-04	2022-Q3		ML	
58406-0455-04	2022-Q4		ML	
58406-0455-04	2023-Q1		ML	
58406-0455-04	2023-Q2		ML	
58406-0456-04	2018-Q3	\$ 1,242.86	ML	
58406-0456-04	2018-Q4	\$ 1,242.86	ML	
58406-0456-04	2019-Q1	\$ 1,319.92	ML	
58406-0456-04	2019-Q2	\$ 1,319.92	ML	
58406-0456-04	2019-Q3	\$ 1,319.92	ML	
58406-0456-04	2019-Q4	\$ 1,319.92	ML	
58406-0456-04	2020-Q1		ML	
58406-0456-04	2020-Q2		ML	
58406-0456-04	2020-Q3		ML	
58406-0456-04	2020-Q4		ML	
58406-0456-04	2021-Q1		ML	
58406-0456-04	2021-Q2		ML	
58406-0456-04	2021-Q3		ML	
58406-0456-04	2021-Q4		ML	
58406-0456-04	2022-Q1		ML	
58406-0456-04	2022-Q2		ML	
58406-0456-04	2022-Q3		ML	
58406-0456-04	2022-Q4		ML	

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
58406-0456-04	2023-Q1		ML	
58406-0456-04	2023-Q2		ML	

Explanations:

[Redacted]

[Redacted]

[Redacted]

[Redacted]

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	58406-0010	2018-Q3		ML	
Y	58406-0010	2018-Q4		ML	
Y	58406-0010	2019-Q1		ML	
Y	58406-0010	2019-Q2		ML	
Y	58406-0010	2019-Q3		ML	
Y	58406-0010	2019-Q4		ML	
Y	58406-0010	2020-Q1		ML	
Y	58406-0010	2020-Q2		ML	
Y	58406-0010	2020-Q3		ML	
Y	58406-0010	2020-Q4		ML	
Y	58406-0010	2021-Q1		ML	
Y	58406-0010	2021-Q2		ML	
Y	58406-0010	2021-Q3		ML	
Y	58406-0010	2021-Q4		ML	
Y	58406-0010	2022-Q1		ML	
Y	58406-0010	2022-Q2		ML	
Y	58406-0010	2022-Q3		ML	
Y	58406-0010	2022-Q4		ML	
Y	58406-0010	2023-Q1		ML	
Y	58406-0010	2023-Q2		ML	

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	58406-0021	2018-Q3		ML	
Y	58406-0021	2018-Q4		ML	
Y	58406-0021	2019-Q1		ML	
Y	58406-0021	2019-Q2		ML	
Y	58406-0021	2019-Q3		ML	
Y	58406-0021	2019-Q4		ML	
Y	58406-0021	2020-Q1		ML	
Y	58406-0021	2020-Q2		ML	
Y	58406-0021	2020-Q3		ML	
Y	58406-0021	2020-Q4		ML	
Y	58406-0021	2021-Q1		ML	
Y	58406-0021	2021-Q2		ML	
Y	58406-0021	2021-Q3		ML	
Y	58406-0021	2021-Q4		ML	
Y	58406-0021	2022-Q1		ML	
Y	58406-0021	2022-Q2		ML	
Y	58406-0021	2022-Q3		ML	
Y	58406-0021	2022-Q4		ML	
Y	58406-0021	2023-Q1		ML	
Y	58406-0021	2023-Q2		ML	

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	58406-0032	2018-Q3		ML	
Y	58406-0032	2018-Q4		ML	
Y	58406-0032	2019-Q1		ML	
Y	58406-0032	2019-Q2		ML	
Y	58406-0032	2019-Q3		ML	
Y	58406-0032	2019-Q4		ML	
Y	58406-0032	2020-Q1		ML	
Y	58406-0032	2020-Q2		ML	
Y	58406-0032	2020-Q3		ML	
Y	58406-0032	2020-Q4		ML	
Y	58406-0032	2021-Q1		ML	
Y	58406-0032	2021-Q2		ML	
Y	58406-0032	2021-Q3		ML	
Y	58406-0032	2021-Q4		ML	
Y	58406-0032	2022-Q1		ML	
Y	58406-0032	2022-Q2		ML	
Y	58406-0032	2022-Q3		ML	
Y	58406-0032	2022-Q4		ML	
Y	58406-0032	2023-Q1		ML	
Y	58406-0032	2023-Q2		ML	

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	58406-0044	2018-Q3		ML	
Y	58406-0044	2018-Q4		ML	
Y	58406-0044	2019-Q1		ML	
Y	58406-0044	2019-Q2		ML	
Y	58406-0044	2019-Q3		ML	
Y	58406-0044	2019-Q4		ML	
Y	58406-0044	2020-Q1		ML	
Y	58406-0044	2020-Q2		ML	
Y	58406-0044	2020-Q3		ML	
Y	58406-0044	2020-Q4		ML	
Y	58406-0044	2021-Q1		ML	
Y	58406-0044	2021-Q2		ML	
Y	58406-0044	2021-Q3		ML	
Y	58406-0044	2021-Q4		ML	
Y	58406-0044	2022-Q1		ML	
Y	58406-0044	2022-Q2		ML	
Y	58406-0044	2022-Q3		ML	
Y	58406-0044	2022-Q4		ML	
Y	58406-0044	2023-Q1		ML	
Y	58406-0044	2023-Q2		ML	

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	58406-0055	2018-Q3		ML	
Y	58406-0055	2018-Q4		ML	
Y	58406-0055	2019-Q1		ML	
Y	58406-0055	2019-Q2		ML	
Y	58406-0055	2019-Q3		ML	
Y	58406-0055	2019-Q4		ML	
Y	58406-0055	2020-Q1		ML	
Y	58406-0055	2020-Q2		ML	
Y	58406-0055	2020-Q3		ML	
Y	58406-0055	2020-Q4		ML	
Y	58406-0055	2021-Q1		ML	
Y	58406-0055	2021-Q2		ML	
Y	58406-0055	2021-Q3		ML	
Y	58406-0055	2021-Q4		ML	
Y	58406-0055	2022-Q1		ML	
Y	58406-0055	2022-Q2		ML	
Y	58406-0055	2022-Q3		ML	
Y	58406-0055	2022-Q4		ML	
Y	58406-0055	2023-Q1		ML	
Y	58406-0055	2023-Q2		ML	

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	58406-0425	2018-Q3		EA	
Y	58406-0425	2018-Q4		EA	
Y	58406-0425	2019-Q1		EA	
Y	58406-0425	2019-Q2		EA	
Y	58406-0425	2019-Q3		EA	
Y	58406-0425	2019-Q4		EA	
Y	58406-0425	2020-Q1		EA	
Y	58406-0425	2020-Q2		EA	
Y	58406-0425	2020-Q3		EA	
Y	58406-0425	2020-Q4		EA	
Y	58406-0425	2021-Q1		EA	
Y	58406-0425	2021-Q2		EA	
Y	58406-0425	2021-Q3		EA	
Y	58406-0425	2021-Q4		EA	
Y	58406-0425	2022-Q1		EA	
Y	58406-0425	2022-Q2		EA	
Y	58406-0425	2022-Q3		EA	
Y	58406-0425	2022-Q4		EA	
Y	58406-0425	2023-Q1		EA	
Y	58406-0425	2023-Q2		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	58406-0435	2018-Q3		ML	
Y	58406-0435	2018-Q4		ML	
Y	58406-0435	2019-Q1		ML	
Y	58406-0435	2019-Q2		ML	
Y	58406-0435	2019-Q3		ML	
Y	58406-0435	2019-Q4		ML	
Y	58406-0435	2020-Q1		ML	
Y	58406-0435	2020-Q2		ML	
Y	58406-0435	2020-Q3		ML	
Y	58406-0435	2020-Q4		ML	
Y	58406-0435	2021-Q1		ML	
Y	58406-0435	2021-Q2		ML	
Y	58406-0435	2021-Q3		ML	
Y	58406-0435	2021-Q4		ML	
Y	58406-0435	2022-Q1		ML	
Y	58406-0435	2022-Q2		ML	
Y	58406-0435	2022-Q3		ML	
Y	58406-0435	2022-Q4		ML	
Y	58406-0435	2023-Q1		ML	
Y	58406-0435	2023-Q2		ML	

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	58406-0445	2018-Q3		ML	
Y	58406-0445	2018-Q4		ML	
Y	58406-0445	2019-Q1		ML	
Y	58406-0445	2019-Q2		ML	
Y	58406-0445	2019-Q3		ML	
Y	58406-0445	2019-Q4		ML	
Y	58406-0445	2020-Q1		ML	
Y	58406-0445	2020-Q2		ML	
Y	58406-0445	2020-Q3		ML	
Y	58406-0445	2020-Q4		ML	
Y	58406-0445	2021-Q1		ML	
Y	58406-0445	2021-Q2		ML	
Y	58406-0445	2021-Q3		ML	
Y	58406-0445	2021-Q4		ML	
Y	58406-0445	2022-Q1		ML	
Y	58406-0445	2022-Q2		ML	
Y	58406-0445	2022-Q3		ML	
Y	58406-0445	2022-Q4		ML	
Y	58406-0445	2023-Q1		ML	
Y	58406-0445	2023-Q2		ML	

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	58406-0455	2018-Q3		ML	
Y	58406-0455	2018-Q4		ML	
Y	58406-0455	2019-Q1		ML	
Y	58406-0455	2019-Q2		ML	
Y	58406-0455	2019-Q3		ML	
Y	58406-0455	2019-Q4		ML	
Y	58406-0455	2020-Q1		ML	
Y	58406-0455	2020-Q2		ML	
Y	58406-0455	2020-Q3		ML	
Y	58406-0455	2020-Q4		ML	
Y	58406-0455	2021-Q1		ML	
Y	58406-0455	2021-Q2		ML	
Y	58406-0455	2021-Q3		ML	
Y	58406-0455	2021-Q4		ML	
Y	58406-0455	2022-Q1		ML	
Y	58406-0455	2022-Q2		ML	
Y	58406-0455	2022-Q3		ML	
Y	58406-0455	2022-Q4		ML	
Y	58406-0455	2023-Q1		ML	
Y	58406-0455	2023-Q2		ML	

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	58406-0456	2018-Q3		ML	
Y	58406-0456	2018-Q4		ML	
Y	58406-0456	2019-Q1		ML	
Y	58406-0456	2019-Q2		ML	
Y	58406-0456	2019-Q3		ML	
Y	58406-0456	2019-Q4		ML	
Y	58406-0456	2020-Q1		ML	
Y	58406-0456	2020-Q2		ML	
Y	58406-0456	2020-Q3		ML	
Y	58406-0456	2020-Q4		ML	
Y	58406-0456	2021-Q1		ML	
Y	58406-0456	2021-Q2		ML	
Y	58406-0456	2021-Q3		ML	
Y	58406-0456	2021-Q4		ML	
Y	58406-0456	2022-Q1		ML	
Y	58406-0456	2022-Q2		ML	
Y	58406-0456	2022-Q3		ML	
Y	58406-0456	2022-Q4		ML	
Y	58406-0456	2023-Q1		ML	
Y	58406-0456	2023-Q2		ML	

Explanations:

[Redacted text block]

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G. Market Data and Revenue and Sales Volume Data

Federal Supply Schedule Price

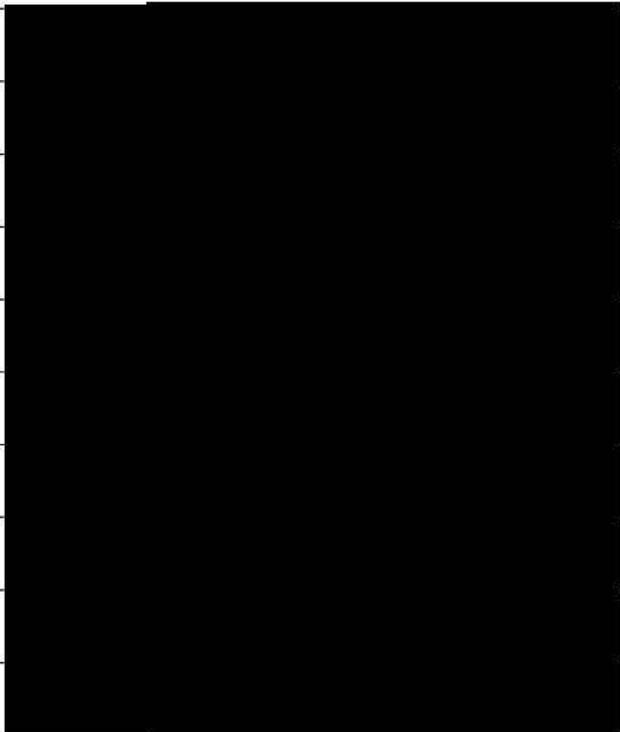
Description: The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. Manufacturers reported any federal supply schedule (FSS) price for the selected drug made available during the most recent five years. The FSS price information 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	58406-0010-04	2019-09-17 - 2019-12-31	\$1,550.17	ML	
Y	58406-0010-04	2020-01-01 - 2020-12-31	\$1,576.68	ML	
Y	58406-0010-04	2021-01-01 - 2021-01-31	\$1,598.28	ML	
Y	58406-0010-04	2021-02-01 - 2021-12-31	\$2,792.15	ML	
Y	58406-0010-04	2022-01-01 - 2022-12-31	\$2,942.64	ML	
Y	58406-0010-04	2023-01-01 - 2023-12-31	\$3,183.94	ML	
Y	58406-0021-04	2019-09-17 - 2019-12-31	\$3,148.70	ML	
Y	58406-0021-04	2020-01-01 - 2020-12-31	\$3,202.54	ML	
Y	58406-0021-04	2021-01-01 - 2021-01-31	\$3,246.42	ML	
Y	58406-0021-04	2021-02-01 - 2021-12-31	\$5,584.30	ML	

G. Market Data and Revenue and Sales Volume Data

Federal Supply Schedule Price

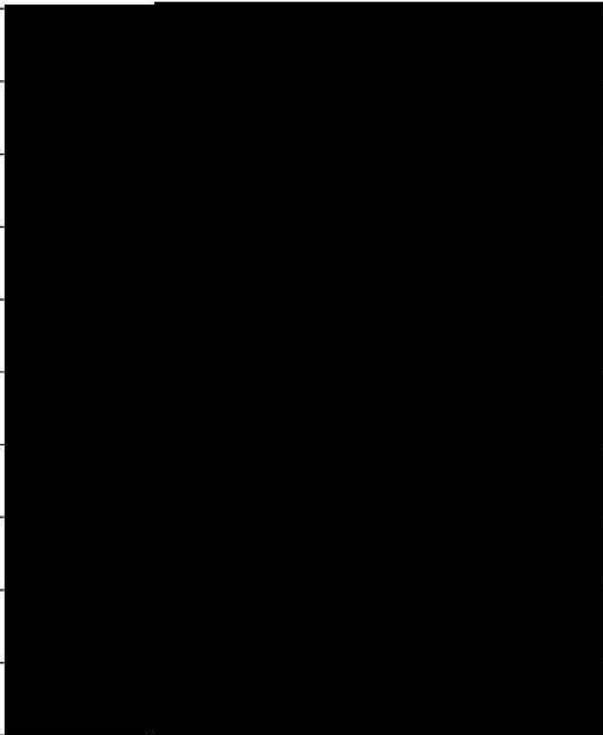
Description: The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. Manufacturers reported any federal supply schedule (FSS) price for the selected drug made available during the most recent five years. The FSS price information 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	58406-0021-04	2022-01-01 - 2022-12-31	\$5,885.30	ML	
Y	58406-0021-04	2023-01-01 - 2023-12-31	\$6,367.89	ML	
Y	58406-0032-04	2019-08-29 - 2019-12-31	\$3,079.07	ML	
Y	58406-0032-04	2020-01-01 - 2020-12-31	\$3,131.72	ML	
Y	58406-0032-04	2021-01-01 - 2021-01-31	\$3,174.62	ML	
Y	58406-0032-04	2021-02-01 - 2021-12-31	\$5,584.30	ML	
Y	58406-0032-04	2022-01-01 - 2022-12-31	\$5,885.30	ML	
Y	58406-0032-04	2023-01-01 - 2023-12-31	\$6,367.89	ML	
Y	58406-0044-04	2020-01-01 - 2020-12-31	\$2,221.05	ML	
Y	58406-0044-04	2021-01-01 - 2021-01-31	\$2,251.48	ML	

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	58406-0044-04	2021-02-01 - 2021-12-31	\$5,584.30	ML	
Y	58406-0044-04	2022-01-01 - 2022-12-31	\$5,885.30	ML	
Y	58406-0044-04	2023-01-01 - 2023-12-31	\$6,367.89	ML	
Y	58406-0055-04	2020-09-25 - 2021-01-31	\$1,576.68	ML	
Y	58406-0055-04	2021-02-01 - 2021-02-14	\$1,998.95	ML	
Y	58406-0055-04	2021-02-15 - 2021-12-31	\$2,792.15	ML	
Y	58406-0055-04	2022-01-01 - 2022-12-31	\$2,942.64	ML	
Y	58406-0055-04	2023-01-01 - 2023-12-31	\$3,183.94	ML	
Y	58406-0425-34	2018-07-01 - 2018-12-31	\$1,067.60	EA	
Y	58406-0425-34	2019-01-01 - 2019-12-31	\$1,581.97	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	58406-0425-34	2020-01-01 - 2020-12-31	\$1,609.03	EA	
Y	58406-0425-34	2021-01-01 - 2021-01-31	\$1,631.07	EA	
Y	58406-0425-34	2021-02-01 - 2021-12-31	\$2,792.15	EA	
Y	58406-0425-34	2022-01-01 - 2022-12-31	\$2,792.15	EA	
Y	58406-0425-34	2023-01-01 - 2023-02-14	\$3,021.11	EA	
Y	58406-0435-04	2018-07-01 - 2018-12-31	\$2,135.21	ML	
Y	58406-0435-04	2019-01-01 - 2019-12-31	\$3,148.70	ML	
Y	58406-0435-04	2020-01-01 - 2020-03-31	\$3,202.54	ML	
Y	58406-0445-04	2018-07-01 - 2018-12-31	\$2,135.21	ML	
Y	58406-0445-04	2019-01-01 - 2019-12-31	\$3,079.07	ML	

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	58406-0445-04	2020-01-01 - 2020-03-31	\$3,131.72	ML	
Y	58406-0455-04	2018-07-01 - 2018-12-31	\$1,067.60	ML	
Y	58406-0455-04	2019-01-01 - 2019-12-31	\$1,550.17	ML	
Y	58406-0455-04	2020-01-01 - 2020-03-31	\$1,576.68	ML	
Y	58406-0456-04	2018-07-01 - 2018-12-31	\$2,088.63	ML	
Y	58406-0456-04	2019-01-01 - 2019-12-31	\$3,584.46	ML	
Y	58406-0456-04	2020-01-01 - 2020-03-31	\$2,221.05	ML	

Explanations:

[Redacted Explanations]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

G. Market Data and Revenue and Sales Volume Data

Big Four Price

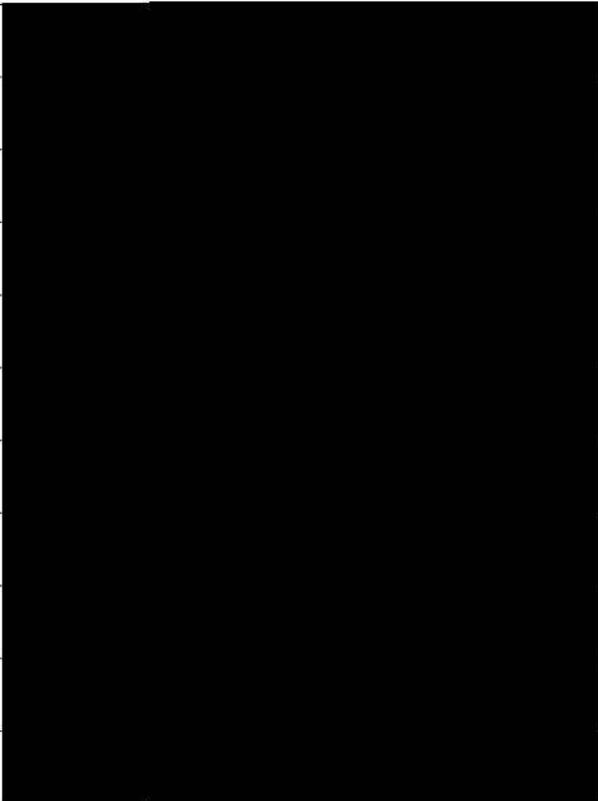
Description: The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Big Four price of the selected drug. The Big Four price information reflects the information that can be 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	58406-0010-04	2019-09-17 - 2019-12-31	1550.17	ML	[REDACTED]
Y	58406-0010-04	2020-01-01 - 2020-12-31	1576.68	ML	[REDACTED]
Y	58406-0010-04	2021-01-01 - 2021-12-31	1598.28	ML	[REDACTED]

G. Market Data and Revenue and Sales Volume Data

Big Four Price

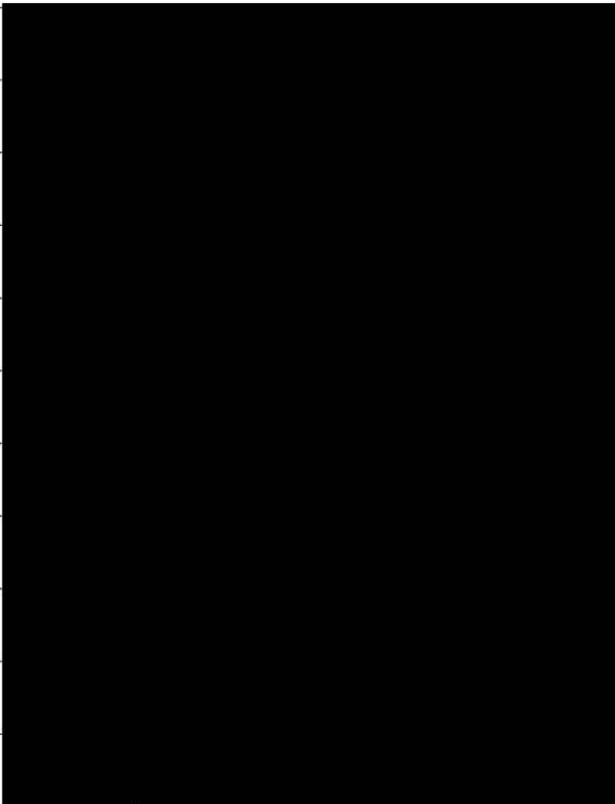
Description: The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Big Four price of the selected drug. The Big Four price information reflects the information that can be 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	58406-0010-04	2022-01-01 - 2022-12-31	2044.17	ML	
Y	58406-0010-04	2023-01-01 - 2023-12-31	2227.29	ML	
Y	58406-0021-04	2019-09-17 - 2019-12-31	3148.7	ML	
Y	58406-0021-04	2020-01-01 - 2020-12-31	3202.54	ML	
Y	58406-0021-04	2021-01-01 - 2021-12-31	3246.42	ML	
Y	58406-0021-04	2022-01-01 - 2022-12-31	4023.05	ML	
Y	58406-0021-04	2023-01-01 - 2023-12-31	4387.73	ML	
Y	58406-0032-04	2019-08-29 - 2019-12-31	3079.07	ML	
Y	58406-0032-04	2020-01-01 - 2020-12-31	3131.72	ML	
Y	58406-0032-04	2021-01-01 - 2021-12-31	3174.62	ML	
Y	58406-0032-04	2022-01-01 - 2022-12-31	4069.45	ML	

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	58406-0032-04	2023-01-01 - 2023-12-31	4451.99	ML	
Y	58406-0044-04	2020-01-01 - 2020-12-31	2221.05	ML	
Y	58406-0044-04	2021-01-01 - 2021-12-31	2251.48	ML	
Y	58406-0044-04	2022-01-01 - 2022-12-31	4118.72	ML	
Y	58406-0044-04	2023-01-01 - 2023-12-31	4490.54	ML	
Y	58406-0055-04	2020-09-25 - 2020-12-31	1576.68	ML	
Y	58406-0055-04	2021-01-01 - 2021-02-14	1576.68	ML	
Y	58406-0055-04	2021-02-15 - 2021-12-31	2076.36	ML	
Y	58406-0055-04	2022-01-01 - 2022-12-31	2184.79	ML	
Y	58406-0055-04	2023-01-01 - 2023-12-31	2284.7	ML	
Y	58406-0425-34	2018-07-01 - 2018-12-31	1067.6	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	58406-0425-34	2019-01-01 - 2019-12-31	1581.97	EA	
Y	58406-0425-34	2020-01-01 - 2020-12-31	1609.03	EA	
Y	58406-0425-34	2021-01-01 - 2021-12-31	1631.07	EA	
Y	58406-0425-34	2022-01-01 - 2022-12-31	2001.97	EA	
Y	58406-0425-34	2023-01-01 - 2023-12-31	2359.83	EA	
Y	58406-0435-04	2018-07-01 - 2018-12-31	2135.21	ML	
Y	58406-0435-04	2019-01-01 - 2019-12-31	3148.7	ML	
Y	58406-0435-04	2020-01-01 - 2020-03-31	3202.54	ML	
Y	58406-0445-04	2018-07-01 - 2018-12-31	2135.21	ML	
Y	58406-0445-04	2019-01-01 - 2019-12-31	3079.07	ML	
Y	58406-0445-04	2020-01-01 - 2020-12-31	3131.72	ML	

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	58406-0455-04	2018-07-01 - 2018-12-31	1067.6	ML	
Y	58406-0455-04	2019-01-01 - 2019-12-31	1550.17	ML	
Y	58406-0455-04	2020-01-01 - 2020-03-31	1576.68	ML	
Y	58406-0456-04	2018-07-01 - 2018-12-31	2018.85	ML	
Y	58406-0456-04	2019-01-01 - 2019-12-31	3584.46	ML	
Y	58406-0456-04	2020-01-01 - 2020-03-31	2221.05	ML	

Explanations:

[Redacted Explanations]



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
58406-0010-04	2018-Q3				ML	
58406-0010-04	2018-Q4				ML	
58406-0010-04	2019-Q1				ML	
58406-0010-04	2019-Q2				ML	
58406-0010-04	2019-Q3				ML	
58406-0010-04	2019-Q4				ML	
58406-0010-04	2020-Q1				ML	
58406-0010-04	2020-Q2				ML	
58406-0010-04	2020-Q3				ML	

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
58406-0010-04	2020-Q4				ML	
58406-0010-04	2021-Q1				ML	
58406-0010-04	2021-Q2				ML	
58406-0010-04	2021-Q3				ML	
58406-0010-04	2021-Q4				ML	
58406-0010-04	2022-Q1				ML	
58406-0010-04	2022-Q2				ML	
58406-0010-04	2022-Q3				ML	
58406-0010-04	2022-Q4				ML	
58406-0010-04	2023-Q1				ML	
58406-0010-04	2023-Q2				ML	
58406-0021-04	2018-Q3				ML	
58406-0021-04	2018-Q4				ML	
58406-0021-04	2019-Q1				ML	
58406-0021-04	2019-Q2				ML	
58406-0021-04	2019-Q3				ML	
58406-0021-04	2019-Q4				ML	
58406-0021-04	2020-Q1				ML	
58406-0021-04	2020-Q2				ML	
58406-0021-04	2020-Q3				ML	

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
58406-0021-04	2020-Q4				ML	
58406-0021-04	2021-Q1				ML	
58406-0021-04	2021-Q2				ML	
58406-0021-04	2021-Q3				ML	
58406-0021-04	2021-Q4				ML	
58406-0021-04	2022-Q1				ML	
58406-0021-04	2022-Q2				ML	
58406-0021-04	2022-Q3				ML	
58406-0021-04	2022-Q4				ML	
58406-0021-04	2023-Q1				ML	
58406-0021-04	2023-Q2				ML	
58406-0032-04	2018-Q3				ML	
58406-0032-04	2018-Q4				ML	
58406-0032-04	2019-Q1				ML	
58406-0032-04	2019-Q2				ML	
58406-0032-04	2019-Q3				ML	
58406-0032-04	2019-Q4				ML	
58406-0032-04	2020-Q1				ML	
58406-0032-04	2020-Q2				ML	
58406-0032-04	2020-Q3				ML	

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
58406-0032-04	2020-Q4				ML	
58406-0032-04	2021-Q1				ML	
58406-0032-04	2021-Q2				ML	
58406-0032-04	2021-Q3				ML	
58406-0032-04	2021-Q4				ML	
58406-0032-04	2022-Q1				ML	
58406-0032-04	2022-Q2				ML	
58406-0032-04	2022-Q3				ML	
58406-0032-04	2022-Q4				ML	
58406-0032-04	2023-Q1				ML	
58406-0032-04	2023-Q2				ML	
58406-0044-04	2018-Q3				ML	
58406-0044-04	2018-Q4				ML	
58406-0044-04	2019-Q1				ML	
58406-0044-04	2019-Q2				ML	
58406-0044-04	2019-Q3				ML	
58406-0044-04	2019-Q4				ML	
58406-0044-04	2020-Q1				ML	
58406-0044-04	2020-Q2				ML	
58406-0044-04	2020-Q3				ML	

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
58406-0044-04	2020-Q4				ML	
58406-0044-04	2021-Q1				ML	
58406-0044-04	2021-Q2				ML	
58406-0044-04	2021-Q3				ML	
58406-0044-04	2021-Q4				ML	
58406-0044-04	2022-Q1				ML	
58406-0044-04	2022-Q2				ML	
58406-0044-04	2022-Q3				ML	
58406-0044-04	2022-Q4				ML	
58406-0044-04	2023-Q1				ML	
58406-0044-04	2023-Q2				ML	
58406-0055-04	2018-Q3				ML	
58406-0055-04	2018-Q4				ML	
58406-0055-04	2019-Q1				ML	
58406-0055-04	2019-Q2				ML	
58406-0055-04	2019-Q3				ML	
58406-0055-04	2019-Q4				ML	
58406-0055-04	2020-Q1				ML	
58406-0055-04	2020-Q2				ML	
58406-0055-04	2020-Q3				ML	

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
58406-0055-04	2020-Q4				ML	
58406-0055-04	2021-Q1				ML	
58406-0055-04	2021-Q2				ML	
58406-0055-04	2021-Q3				ML	
58406-0055-04	2021-Q4				ML	
58406-0055-04	2022-Q1				ML	
58406-0055-04	2022-Q2				ML	
58406-0055-04	2022-Q3				ML	
58406-0055-04	2022-Q4				ML	
58406-0055-04	2023-Q1				ML	
58406-0055-04	2023-Q2				ML	
58406-0425-34	2018-Q3				EA	
58406-0425-34	2018-Q4				EA	
58406-0425-34	2019-Q1				EA	
58406-0425-34	2019-Q2				EA	
58406-0425-34	2019-Q3				EA	
58406-0425-34	2019-Q4				EA	
58406-0425-34	2020-Q1				EA	
58406-0425-34	2020-Q2				EA	
58406-0425-34	2020-Q3				EA	

G. Market Data and Revenue and Sales Volume Data

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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
58406-0425-34	2020-Q4				EA	
58406-0425-34	2021-Q1				EA	
58406-0425-34	2021-Q2				EA	
58406-0425-34	2021-Q3				EA	
58406-0425-34	2021-Q4				EA	
58406-0425-34	2022-Q1				EA	
58406-0425-34	2022-Q2				EA	
58406-0425-34	2022-Q3				EA	
58406-0425-34	2022-Q4				EA	
58406-0425-34	2023-Q1				EA	
58406-0425-34	2023-Q2				EA	
58406-0435-04	2018-Q3				ML	
58406-0435-04	2018-Q4				ML	
58406-0435-04	2019-Q1				ML	
58406-0435-04	2019-Q2				ML	
58406-0435-04	2019-Q3				ML	
58406-0435-04	2019-Q4				ML	
58406-0435-04	2020-Q1				ML	
58406-0435-04	2020-Q2				ML	
58406-0435-04	2020-Q3				ML	

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
58406-0435-04	2020-Q4				ML	
58406-0435-04	2021-Q1				ML	
58406-0435-04	2021-Q2				ML	
58406-0435-04	2021-Q3				ML	
58406-0435-04	2021-Q4				ML	
58406-0435-04	2022-Q1				ML	
58406-0435-04	2022-Q2				ML	
58406-0435-04	2022-Q3				ML	
58406-0435-04	2022-Q4				ML	
58406-0435-04	2023-Q1				ML	
58406-0435-04	2023-Q2				ML	
58406-0445-04	2018-Q3				ML	
58406-0445-04	2018-Q4				ML	
58406-0445-04	2019-Q1				ML	
58406-0445-04	2019-Q2				ML	
58406-0445-04	2019-Q3				ML	
58406-0445-04	2019-Q4				ML	
58406-0445-04	2020-Q1				ML	
58406-0445-04	2020-Q2				ML	
58406-0445-04	2020-Q3				ML	

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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58406-0445-04	2020-Q4				ML	
58406-0445-04	2021-Q1				ML	
58406-0445-04	2021-Q2				ML	
58406-0445-04	2021-Q3				ML	
58406-0445-04	2021-Q4				ML	
58406-0445-04	2022-Q1				ML	
58406-0445-04	2022-Q2				ML	
58406-0445-04	2022-Q3				ML	
58406-0445-04	2022-Q4				ML	
58406-0445-04	2023-Q1				ML	
58406-0445-04	2023-Q2				ML	
58406-0456-04	2018-Q3				ML	
58406-0456-04	2018-Q4				ML	
58406-0456-04	2019-Q1				ML	
58406-0456-04	2019-Q2				ML	
58406-0456-04	2019-Q3				ML	
58406-0456-04	2019-Q4				ML	
58406-0456-04	2020-Q1				ML	
58406-0456-04	2020-Q2				ML	
58406-0456-04	2020-Q3				ML	

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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
58406-0456-04	2020-Q4				ML	
58406-0456-04	2021-Q1				ML	
58406-0456-04	2021-Q2				ML	
58406-0456-04	2021-Q3				ML	
58406-0456-04	2021-Q4				ML	
58406-0456-04	2022-Q1				ML	
58406-0456-04	2022-Q2				ML	
58406-0456-04	2022-Q3				ML	
58406-0456-04	2022-Q4				ML	
58406-0456-04	2023-Q1				ML	
58406-0456-04	2023-Q2				ML	
58406-0455-04	2018-Q3				ML	
58406-0455-04	2018-Q4				ML	
58406-0455-04	2019-Q1				ML	
58406-0455-04	2019-Q2				ML	
58406-0455-04	2019-Q3				ML	
58406-0455-04	2019-Q4				ML	
58406-0455-04	2020-Q1				ML	
58406-0455-04	2020-Q2				ML	
58406-0455-04	2020-Q3				ML	

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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58406-0455-04	2020-Q4				ML	
58406-0455-04	2021-Q1				ML	
58406-0455-04	2021-Q2				ML	
58406-0455-04	2021-Q3				ML	
58406-0455-04	2021-Q4				ML	
58406-0455-04	2022-Q1				ML	
58406-0455-04	2022-Q2				ML	
58406-0455-04	2022-Q3				ML	
58406-0455-04	2022-Q4				ML	
58406-0455-04	2023-Q1				ML	
58406-0455-04	2023-Q2				ML	

Explanations:

[Redacted Explanations]

[Redacted Explanations]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Manufacturer E2 Submission - Amgen



Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	ETANERCEPT
	Respondent Name	Nell Mitchell
	Organization Name (if applicable)	Amgen
	Respondent Email	nmitch01@amgen.com
	Who is completing this form?	
Question 27: Prescribing Information	Prescribing Information	<p>The evidence referenced in this section ranges from 2017 to 2023.</p> <p>Indications: Enbrel®(etanercept), a tumor necrosis factor (TNF) blocker, is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75 kilodalton (p75) tumor necrosis factor receptor (TNFR) linked to the Fc portion of human IgG1. Amgen has continually invested in Enbrel, devoting significant funding and decades of research toward its expansion into new indications. Enbrel was first approved in 1998 for rheumatoid arthritis, followed by polyarticular juvenile idiopathic arthritis in 1999, psoriatic arthritis (PsA) in 2002, ankylosing spondylitis in 2003, plaque psoriasis in 2004, and pediatric plaque psoriasis in 2016. Most recently in December 2022, a new application was submitted for an efficacy supplement in juvenile PsA. Enbrel is indicated for the following:</p> <ul style="list-style-type: none"> - Rheumatoid Arthritis (RA): Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active RA. Enbrel can be initiated in combination with methotrexate (MTX) or used alone. - Psoriatic Arthritis (PsA): Reducing signs and symptoms, inhibiting the progression of structural damage of active arthritis, and improving physical function in patients with PsA. Enbrel can be used with or without MTX. - Plaque Psoriasis (PsO): The treatment of patients 4 years or older with chronic moderate to severe PsO who are candidates for systemic therapy or phototherapy. - Ankylosing Spondylitis (AS): Reducing signs and symptoms in patients with active AS. -Polyarticular Juvenile Idiopathic Arthritis (JIA): Reducing signs and symptoms of moderately to severely active JIA in patients ages 2 and older. <p>The most relevant indications for Medicare are RA, PsA, PsO, and AS.</p> <p>Dosage and Administration: Administration of one 50 mg Enbrel single-dose prefilled syringe, one single-dose prefilled Enbrel SureClick® autoinjector, or one Enbrel Mini single-dose prefilled cartridge (for use with the AutoTouch® reusable autoinjector only), provides a dose equivalent to two 25 mg Enbrel single-dose prefilled syringes, two 25 mg single-dose vials, or two multiple-dose vials of lyophilized Enbrel, when multiple-dose vials are</p>



Question	Sub-Question	Response
		<p>reconstituted and administered as recommended. The recommended dosage strength and frequency is 50 mg weekly for adult RA, AS, and PsA and 50 mg twice weekly for 3 months followed by 50 mg once weekly (maintenance) for adult PsO. In the case of pediatric patients weighing less than 138lbs, a weekly dose of 0.8mg/kg is advised. For pediatric patients weighing 138lbs or more, a weekly dose of 50 mg is recommended. Methotrexate, glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs (NSAIDs), or analgesics may be continued during treatment with Enbrel.</p> <p>Adverse reactions: Patients treated with Enbrel are at risk of developing serious infections that may lead to hospitalization or death. Other serious adverse reactions include malignancies, neurological events, hematologic events, congestive heart failure, hepatitis B virus (HBV) reactivation, allergic reactions, lupus-like syndrome, and autoimmune hepatitis. It is recommended for providers to exercise caution when considering the use of Enbrel in patients with preexisting or recent-onset central or peripheral nervous system demyelinating disorders. Discontinuation of Enbrel should be considered in patients with confirmed significant hematologic abnormalities. Enbrel is contraindicated in patients with sepsis. The most common adverse reactions with Enbrel were infections and injection site reactions.</p> <p>As with all therapeutic proteins, there is potential for immunogenicity. Antibodies to the TNF receptor portion or other protein components of the Enbrel drug product were detected at least once in sera of approximately 6% of adult patients with RA, PsA, AS or PsO. These antibodies were all non-neutralizing. In adult PsO studies that evaluated the exposure of Enbrel for up to 120 weeks, the percentage of patients testing positive at the assessed time points of 24, 48, 72, and 96 weeks ranged from 3.6% to 8.7% and were all non-neutralizing. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay and may be influenced by assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. In considering therapeutic alternatives, CMS should use a group of therapeutics most similar to Enbrel. This would constitute the group of TNF inhibitors – adalimumab, certolizumab pegol, golimumab and infliximab – grouped as a market basket for Enbrel’s therapeutic alternative. This grouping of therapeutic alternatives would constitute the group with a similar mechanism of action, indications, and evidence base.</p> <p>Therapeutic alternatives prescribing information for indications shared with Enbrel:</p> <p>TNF inhibitors (TNFi) adalimumab (Humira®) [1]: - Indicated for: adult patients with moderate-to-severe RA, moderate-to-severe JIA in patients 2 years of age and older, adult patients with active PsA, adult patients with active AS, adult patients with moderate-to-severe chronic PsO who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate</p>



Question	Sub-Question	Response
		<p>- Adverse reactions (>10%): infections, injection site reactions, headache, and rash</p> <p>infliximab (Remicade®) [2] - Indicated for: adult patients with moderate-to-severe RA in combination with methotrexate, active AS, active PsA in adults, chronic severe PsO in adult patients who are candidates for systemic therapy and when other systemic therapies are medically less appropriate - Adverse reactions (>10%): infections, infusion-related reactions, headache, and abdominal pain</p> <p>golimumab (Simponi®) [3] and (Simponi Aria®) [4] - Indicated for: adult patients with moderate-to-severe RA in combination with methotrexate, adult patients with active PsA alone or in combination with methotrexate, adult patients with active AS - Adverse reactions (> 5%): upper respiratory tract infection, nasopharyngitis</p> <p>certolizumab pegol (Cimzia®) [5] - Indicated for: adults with moderate-to-severe RA, adults with active PsA, adults with active AS, moderate-to-severe PsO in adults who are candidates for systemic therapy or phototherapy - Adverse reactions (≥7%): upper respiratory tract infection, rash, and urinary tract infection</p> <p>Other non-TNFi biologics/oral small molecules (OSM) abatacept (Orencia®) [6] - Indicated for: adults with moderate-to-severe RA, patients 2 years of age and older with moderate-to-severe polyarticular JIA, adults with active PsA - Adverse reactions (10%): headache, upper respiratory tract infection, nasopharyngitis, and nausea</p> <p>tocilizumab (Actemra®) [7] - Indicated for: moderate-to-severe RA in adults with inadequate response to one or more disease modifying antirheumatic drugs (DMARDs), patients 2 years of age and older with active polyarticular JIA or active systemic JIA - Adverse reactions (5%): upper respiratory tract infections, nasopharyngitis, headache, hypertension, increased ALT, injection site reactions</p> <p>sarilumab (Kevzara®) [8] - Indicated for: moderate-to-severe RA in adults with an inadequate response or intolerance to one or more DMARDs - Adverse reactions (3%): neutropenia, increased ALT, injection site erythema, upper respiratory infections, and urinary tract infections</p>



Question	Sub-Question	Response
		<p>rituximab (Rituxan®) [9] - Indicated for: moderate-to-severe RA in combination with methotrexate in adults with an inadequate response to one or more TNF antagonist therapies - Adverse reactions (10%): upper respiratory tract infection, nasopharyngitis, urinary tract infection, and bronchitis (other important adverse reactions include infusion-related reactions, serious infections, and cardiovascular events)</p> <p>tofacitinib (Xeljanz®) [10]/(Xeljanz XR®) [11] - Indicated for: moderate-to-severe RA in adult patients with an inadequate response or intolerance to one or more TNF blockers, active PsA in adult patients with an inadequate response or intolerance to one or more TNF blockers, active AS in adult patients with an inadequate response or intolerance to one or more TNF blockers, and polyarticular JIA in patients 2 years of age and older with an inadequate response or intolerance to one or more TNF blockers (not recommended in combination with biologic DMARDs or potent immunosuppressants in any of these indications) - Adverse reactions (>2%): upper respiratory tract infection, nasopharyngitis, diarrhea, and headache</p> <p>baricitinib (Olumiant®) [12] - Indicated for: moderate-to-severe RA in adults with an inadequate response to one or more TNF blockers (not recommended for use in combination with other JAK inhibitors, biologic DMARDs, or potent immunosuppressants) - Adverse reactions (≥1%): upper respiratory tract infections, nausea, herpes simplex, and herpes zoster</p> <p>upadacitinib (Rinvoq®) [13] - Indicated for: moderate-to-severe RA in adults with an inadequate response or intolerance to one or more TNF blockers, active PsA in adults with an inadequate response or intolerance to one or more TNF blockers, and active AS in adults with an inadequate response or intolerance to one or more TNF blockers (not recommended for use in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants in any indication) - Adverse reactions (≥ 1%): upper respiratory tract infections, herpes zoster, herpes simplex, bronchitis, nausea, cough, pyrexia, acne, and headache</p> <p>brodalumab (Siliq®) [14] - Indicated for: moderate-to-severe PsO in patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies - Adverse reactions (≥1%): arthralgia, headache, fatigue, diarrhea, oropharyngeal pain, nausea, myalgia, injection site reactions, influenza, neutropenia, and tinea infection</p>



Question	Sub-Question	Response
		<p>guselkumab (Tremfya®) [15] - Indicated for: moderate-to-severe PsO in adult patients who are candidates for systemic therapy or phototherapy, adults with active PsA - Adverse reactions (≥1%): upper respiratory infections, headache, injection site reactions, arthralgia, bronchitis, diarrhea, gastroenteritis, tinea infections, and herpes simplex infections</p> <p>tildrakizumab (Ilumya®) [16] - Indicated for: moderate-to-severe PsO in adults who are candidates for systemic therapy or phototherapy - Adverse reactions (≥1%): upper respiratory infections, injection site reactions, and diarrhea</p> <p>ustekinumab (Stelara®) [17] - Indicated for: moderate-to-severe PsO in adults and pediatric patients 6 years and older who are candidates for phototherapy or systemic therapy, active PsA in adults and pediatric patients 6 years and older - Adverse reactions (PsO ≥3%): nasopharyngitis, upper respiratory tract infection, headache, and fatigue</p> <p>secukinumab (Cosentyx®) [18] - Indicated for: moderate-to-severe PsO in patients 6 years and older who are candidates for systemic therapy or phototherapy, active PsA in patients 2 years of age and older, active AS in adults - Adverse reactions (> 1%): nasopharyngitis, diarrhea, and upper respiratory tract infection</p> <p>ixekizumab (Taltz®) [19] - Indicated for: moderate-to-severe PsO in patients 6 years and older who are candidates for systemic therapy or phototherapy, active PsA in adults, active AS in adults - Adverse reactions (≥1%): injection site reactions, upper respiratory tract infections, nausea, and tinea infections</p> <p>risankizumab-rzaa (Skyrizi®) [20] - Indicated for: moderate-to-severe PsO in adults who are candidates for systemic therapy or phototherapy, active PsA in adults - Adverse reactions (≥1%): upper respiratory infections, headache, fatigue, injection site reactions, and tinea infections</p> <p>Course of care: More than 600 distinct therapy sequences have been observed for the course of care for moderate to severe RA. This underscores the vital importance of having a wide range of therapeutic choices for patients in this population. For Enbrel across all populations, the distribution of use is RA – 66%; PSA – 17%; PSO – 8%; AS – 7% (Ref: Amgen Data on File). In RA, Enbrel is considered a first-line biologic if low disease activity (LDA) is not achieved</p>



Question	Sub-Question	Response
		<p>with MTX. Nearest comparators for this indication include the TNFi adalimumab, certolizumab pegol, golimumab, and infliximab. Other biologic disease-modifying antirheumatic drugs (bDMARDs) such as the T-cell costimulatory inhibitor abatacept; IL-6 receptor inhibitors including tocilizumab and sarilumab; anti-CD20 antibody rituximab; and targeted synthetic DMARDs (tsDMARDs) JAK inhibitors such as tofacitinib, baricitinib, and upadacitinib are also used in rheumatoid arthritis [21].</p> <p>For DMARD-naïve moderate to severe RA patients, methotrexate (MTX) is the recommended first line therapy as stated in the American College of Rheumatology (ACR) guidelines [21]. Other conventional synthetic DMARDs (csDMARDs) can be used or added to MTX prior to advancing to the biologics; however, these therapies are challenging for patients to take, and compliance is often low.</p> <p>Using the longitudinal CorEvitas RA Registry, researchers traced practice patterns across 6,015 patients between January 2012 to December 2021 [22]. During this time, the use of TNFi as first line biologic/targeted synthetic (b/ts) DMARD after MTX declined from 80% to 66%. While most other biologic use remained relatively stable after MTX, the use of tsDMARD increased to almost 20%. Patients used between one to six different lines of b/ts DMARD therapy with 43% using at least three different therapy lines. Most patients started a TNFi as either monotherapy or in combination with MTX.</p> <p>For the second line of therapy, the predominant practice pattern was for TNFi-MTX combination therapy patients to drop MTX and continue TNFi monotherapy. If patients stopped a TNFi, they generally restarted a TNFi or other b/ts DMARD within a few months. In patients who had taken three or more lines of therapy and initiated first line combination of TNFi plus MTX or TNFi monotherapy, the second line was most often a switch to a second TNFi, MTX monotherapy, or no therapy. Duration of lines of therapy during the 2018-2021 time period were 153, 108, and 117 days for therapy lines one, two and three, respectively. Overall, there were over 600 different lines of therapy sequences. The need for therapeutic options remains critical in this patient population as many patients change therapies for efficacy, safety, tolerability, and cost reasons.</p> <p>For treatment-naïve active PsA patients, guidelines suggest TNFi like Enbrel are preferred first-line therapy except in patients who prefer an oral drug or have contraindications [23]. Guidelines recommend TNFi over oral small molecules (OSMs) (methotrexate, sulfasalazine, cyclosporine, leflunomide, apremilast) or an IL-17i or IL-12/23i biologic (ustekinumab, secukinumab, ixekizumab, brodalumab). Other TNFi include infliximab, adalimumab, golimumab, and certolizumab pegol. A TNFi is the preferred second-line therapy if active disease persists following first-line treatment with an OSM or a prior TNFi.</p> <p>Enbrel is recommended as a first-line monotherapy for moderate-to-severe plaque psoriasis, and plaque psoriasis of</p>



Question	Sub-Question	Response
		<p>any severity when associated with significant PsA. Enbrel may be combined with topicals, MTX, acitretin, narrowband UV phototherapy, and cyclosporine where clinically indicated. Other recommended FDA-approved TNFis include adalimumab, certolizumab, and infliximab [24].</p> <p>References</p> <p>[1] Humira® [package insert]. North Chicago, IL: AbbVie Inc.; 2021. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125057s417lbl.pdf#page=60</p> <p>[2] Remicade® [package insert]. Horsham, PA: Janssen Biotech, Inc.; 2021. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/103772s5401lbl.pdf</p> <p>[3] Simponi® [package insert]. Horsham, PA: Janssen Biotech, Inc.; 2018. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/125289s150lbl.pdf</p> <p>[4] Simponi Aria® [package insert]. Horsham, PA: Janssen Biotech, Inc.; 2020. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125433s032lbl.pdf</p> <p>[5] Cimzia® [package insert]. Smyrna, GA: UCB, Inc.; 2020. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/125160s305lbl.pdf</p> <p>[6] Orencia® [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2017. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125118s240lbl.pdf</p> <p>[7] Actemra® [package insert]. South San Francisco, CA: Genentech, Inc.; 2022. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/125276s138lbl.pdf</p> <p>[8] Kevzara® [package insert]. Bridgewater, NJ: Sanofi-Aventis U.S. LLC.; 2023. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761037s013lbl.pdf</p> <p>[9] Rituxan® [package insert]. South San Francisco, CA: Genentech, Inc.; 2021. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/103705s5467lbl.pdf</p> <p>[10] Xeljanz® [package insert]. New York, NY: Pfizer, Inc.; 2020. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/203214s028,208246s013,213082s003lbl.pdf</p> <p>[11] Xeljanz XR® [package insert] New York, NY: Pfizer, Inc.; 2020. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/203214s028,208246s013,213082s003lbl.pdf</p> <p>[12] Olumiant® [package insert]. Indianapolis, IN: Lilly USA, LLC.; 2022. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/207924s007lbl.pdf</p> <p>[13] Rinvoq® [package insert]. North Chicago IL: AbbVie Inc.; 2023. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/211675s017lbl.pdf</p> <p>[14] Siliq® [package insert]. Grand Duchy of Luxembourg, Luxembourg: Valeant Pharmaceuticals international, Inc.; 2017. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761032lbl.pdf</p> <p>[15] Tremfya® [package insert] Horsham, PA: Janssen Biotech, Inc.; 2023. Available from: https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/TREMFYA-pi.pdf</p>



Question	Sub-Question	Response
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	Evidence Submitted include a cost-effectiveness measure?	N



Question	Sub-Question	Response
	What type of Evidence is shown?	
Question 28: Therapeutic Impact and Comparative Effectiveness	Therapeutic Impact and Comparative Effectiveness	<p>The evidence referenced in this section ranges from 1993 to 2023.</p> <p>Introduction</p> <p>Enbrel is a first-in-class treatment for certain inflammatory conditions that has brought value across the health system. Enbrel is highly effective in inhibiting the progression of structural joint damage, improving physical function, increasing work productivity, and reducing pain in moderate to severe rheumatoid arthritis (RA), its main indication, with similar, rapid impacts in elderly and younger patients [1]. RA is a debilitating chronic condition, involving painful swelling at the joints, long-term bone erosion, and joint deformation [1]. Across Enbrel’s indicated disease areas, RA patients account for 66% of its utilization with: PSA – 17%, PSO – 8%, AS – 7% (data on file).</p> <p>Rheumatoid Arthritis</p> <p>Enbrel brings value to patients and has demonstrated impressive clinical outcomes. Numerous RA “effectiveness” studies, including a study of Medicare patients, found that Enbrel has the highest proportion of effectively treated patients versus other therapeutic alternatives [2,3]. Enbrel has led to rapid improvements in clinical outcomes and patient-reported Health Assessment Questionnaire-Disability Index (HAQ-DI) scores [1,4]. Enbrel also remains a critical treatment option for patients failing adalimumab [5].</p> <p>Efficacy/Clinical Impact & Comparative Effectiveness</p> <p>A primary goal of moderate to severe RA therapy is achieving remission or low-disease activity (LDA) (based on Disease Activity Score in 28 joints [DAS28]), which Enbrel has a proven record of accomplishing and maintaining in both early and longstanding moderate to severe RA patients [6]. In LDA, patients experience little to no pain, minimal to no joint swelling, and halted joint damage as measured by radiographs. In long-term trials with partial Medicare populations, 55% of the Enbrel group had no radiographic progression through 5 years, indicating long-term treatment prevents further joint damage [4]. In registrational or key clinical trials (Table 1), Enbrel has demonstrated meaningful improvements in the RA ACR Response criteria, a measure of multiple disease components including tender/swollen joints, patient pain, physical functioning, patient and physician global assessments, and acute-phase reactant value [7]. The FDA has used the ACR 20 response, representing at least 20% improvement, as the primary endpoint in evaluating clinical trial success for approval and labeling. This measurement is also evaluated at the 50% and 70% improvement levels.</p> <p>Enbrel is an important option for patients looking to avoid or withdraw methotrexate (MTX) or switch after adalimumab failure. In a study in early rheumatoid arthritis patients (some aged 65+) who had never taken a csDMARD or MTX, Enbrel monotherapy led to greater proportions of patients achieving ACR 20/50/70 as well as</p>



Question	Sub-Question	Response
		<p>fewer adverse reactions and infections compared to MTX monotherapy [4]. Additionally, Enbrel monotherapy was associated with maintenance of remission (simplified disease activity index (SDAI) score ≤ 3.3) following withdrawal of MTX [8]. This makes Enbrel a much-needed option for reducing treatment burden, since within 6 months to 2 years, approximately half of RA patients discontinue MTX due to poor tolerability and side effects like hepatotoxicity, fibrosis, cirrhosis of liver and gastrointestinal toxicity [9]. Enbrel’s efficacy, safety, and tolerability have made it a preferred therapy in RA patients who have failed MTX. A single arm trial in adalimumab failure patients including Medicare patients (21%) found Enbrel to be particularly effective in quickly achieving ACR 20, with improvements in patient-reported disability and pain, SDAI, and mean swollen joint count in 35.7% of patients; this supports Enbrel’s role as a compelling alternative for patients looking to switch off adalimumab [5].</p> <p>Enbrel emerged as one of the most effective treatment options in two separate network meta-analysis (NMA) studies, demonstrating its value both as a combination therapy and monotherapy for rheumatoid arthritis. In an NMA by a non-profit organization (Tables 2, 3), targeted immune modulators (TIM, aka b/ts DMARDs) for moderate-to-severe RA were ranked by efficacy in achieving ACR response. Among the TIM/MTX combination regimens, Enbrel displayed a greater likelihood in achieving ACR response compared to other TIMs. In the monotherapy category, Enbrel ranked second in achieving ACR response compared to other TIMs [10]. A different NMA analysis of 46 randomized controlled trials (RCTs) with 14,049 total patients found only monotherapy Enbrel (standard dose) offered an improvement over MTX, while most other biologic monotherapies were only an improvement over MTX with a high dose regimen. Additionally, for patients with established RA, only standard dose Enbrel was associated with statistically significant and clinically meaningful improvements in HAQ-DI scores whereas all other biologic monotherapy regimens had no significant difference [11]. Outcomes of another NMA provide evidence of Enbrel having greater efficacy than adalimumab, infliximab, and golimumab. Also, the analysis showed that Enbrel achieved greater improvement in the HAQ-DI (patient disability) than other evaluated treatments [12].</p> <p>Enbrel had the highest proportion of “effectively” treated patients in a comparative effectiveness analysis versus adalimumab, infliximab, and abatacept (24% for adalimumab, 28% for Enbrel, 23% for infliximab, 26% for abatacept). This large claims-based analysis of 14,244 Medicare beneficiaries with moderate to severe RA used a validated algorithm to identify LDA or remission (DAS-28) [13]. To determine if a patient’s treatment was “effective,” the algorithm used six criteria: high adherence, no increase in biologic dose or frequency, no biologic switch, no new DMARD, no new chronic oral glucocorticoid or dose increase, and limited multiple joint injections [14]. This same algorithm has been applied to a large commercial claims database, which found similar results where the percent of “effectively” treated patients was highest in Enbrel [3].</p> <p>Enbrel’s impressive clinical outcomes are matched by life-changing benefits to patient well-being and functional health, as demonstrated by improved HAQ-DI scores [1,15]. A post-hoc analysis of Enbrel clinical trials and open-label extensions in RA found that mean improvements from baseline in HAQ-DI ranged from 0.39-0.92 points (on a 3-point scale, minimum clinically important difference [MCID] is 0.22 in RA) in patients aged 65+ and 0.57-1.00 points in younger patients; these were maintained through the open-label extension trials for up to 6 years [1].</p>



Question	Sub-Question	Response
		<p>Increasingly more Medicare patients work full or part time, and Enbrel has demonstrated a reduction in work impairment, absenteeism, and presenteeism, gaining patients a projected 284.5 yearly work productivity hours [16].</p> <p>Safety</p> <p>Enbrel has more safety data and years of patient exposure than most other biologics (data on file). Its established safety in RA provides a well-understood profile. Furthermore, Amgen’s commitment to innovations that improve the patient experience has yielded tangible, meaningful benefits that better patient lives [17].</p> <p>With extensive clinical research data and post-marketing surveillance in RA, Enbrel has a well-studied, well-understood safety profile. Additionally, the safety profile of Enbrel in elderly RA patients was found to be similar to that of younger RA patients on Enbrel [18]. Long-term safety has been confirmed beyond 10 years, which is especially important given the chronic nature of RA [6].</p> <p>Enbrel has an established safety profile in RA. In the ERA trial, Enbrel patients were found to experience a lower rate of adverse reactions compared to MTX patients, with the latter having a higher rate of all infections [4]. In the real-world setting, Enbrel has demonstrated lower rates of adverse reactions than infliximab and adalimumab, with one analysis finding Enbrel having 12 adverse reactions per 100 people per year versus 24 for infliximab and 22 for adalimumab [19]. Fewer Enbrel patients require use in combination with MTX than other biologics, potentially avoiding the additional MTX-related side effects [20]. In addition to Enbrel’s tolerability and consistent dosing without needing dose escalation, the lower MTX combination use may help explain what one analysis found as patients’ comparatively higher adherence to Enbrel [21]. Compared to adalimumab and infliximab, Enbrel had the highest drug survival rates at 3 and 4 years, the lowest discontinuation incidence per 100 person-years in RA, and the highest median retention as the 1st and 2nd line therapy according to two analyses [22,23].</p> <p>Amgen continued to invest and innovate to explore new ways to improve the patient experience including a low pain formulation, Enbrel Mini™ with AutoTouch®, a patient feedback tool, and the Enbrel Nurse Partner [17]. A Phase 3b randomized double-blind study found that RA and PsA patients experienced statistically significant lower mean injection site pain with the new phosphate-free formulation of Enbrel versus the prior formulation [17]. Pain related to injection is a key reason for discontinuing biologic DMARD therapy: 41% of RA patients highlight this as the first or second reason they have stopped biologic therapy [24]. Pain is an important outcome for patients and affects long-term compliance of medication, which can dramatically improve RA and PsA outcomes. Additionally, Amgen has invested in patient-centered resources to address patient compliance challenges, including innovative first in class auto-injectors like the Enbrel Mini with AutoTouch, and the Enbrel Nurse Partner Program [17]. Enbrel Nurse Partners offer one-on-one support for patients, answering questions on the product and resources that may help lower out-of-pocket costs.</p> <p>Value</p> <p>Enbrel has been proven to generate economic value for the US health system. Studies representing nearly 30,000 patients differentiate Enbrel as having the lowest cost per effectively treated RA patient compared to therapeutic alternatives in both Medicare and commercial populations [2,13]. Additionally, patients on Enbrel displayed higher</p>



Question	Sub-Question	Response
		<p>persistence and less dose escalation which translated to overall lower drug costs [2,3,25,26]. Comparing clinical costs of Enbrel, infliximab, adalimumab, and abatacept, Enbrel demonstrated the greatest “effectiveness” and lowest cost per effectively treated patient in a Medicare analysis [13]. This outcome has been consistently reinforced across numerous studies in diverse RA patient populations, including a multistate Medicaid study [27], which have found adalimumab to be 114% more costly than Enbrel for newly-initiated and continuing RA patients [2,3,25,26,28,29]. One analysis of U.S. commercial claims for 14,775 patients found Enbrel had a lower cost per effectively treated patient compared to adalimumab, making it one of the most cost-effective alternatives to conventional DMARDs [2]. It found that the cost per effectively treated patient with Enbrel compared to adalimumab was approximately \$10K lower in first-line and about \$60K lower in second-line. Additionally, across second-line therapies, Enbrel had a lower cost than other TNFis: abatacept \$174,090; adalimumab \$154,540; certolizumab pegol \$236,743; Enbrel \$94,821; golimumab \$140,651; infliximab \$185,369; tocilizumab \$109,351; and tofacitinib \$130,501.</p> <p>Importantly, several analyses have found that patients initiating Enbrel as their first biologic tend to be more persistent and switch less, suggesting improved outcomes and avoiding additional costs, disruptions, and side effects associated with switching [2,3,25,26,28,29,30]. Among both persistent patients and those who switch, patients who initiated biologic therapy with Enbrel had lower 1-year total health care costs than patients who initiated therapy with another biologic [30].</p> <p>Enbrel dosing can be more predictable than other TNFis; as Enbrel patients tend to have lower rates of dose escalation than patients taking infliximab or adalimumab, which translates to lower drug costs, RA-related costs, and total costs [31]. The greater proportion of effectively treated patients and associated lower costs with Enbrel are due to its lower rates of dose escalation compared to infliximab and adalimumab, which have labeling that allows for dose escalation, unlike Enbrel [31]. An analysis of large commercial and Medicare Supplemental databases showed that in moderate to severe RA, 1.2% of Enbrel patients versus 10.6% of adalimumab patients had received at least a 100% dose increase from the starting dose at 19 to 24 months, and adalimumab costs-per-patient-per-month were 11.4% higher than Enbrel’s over 1 year (data on file).</p> <p>Unlike its monoclonal antibody comparators, adalimumab and infliximab, Enbrel is not known to develop neutralizing anti-drug antibodies (dependent on assay sensitivity and specificity). This finding may contribute to Enbrel’s greater dose stability in RA. Across multiple retrospective studies, patients treated with Enbrel had stable dosing of 93.1% to 99.2% compared with 66.4% to 92.2% of patients treated with adalimumab and 40.0% to 83.6% of patients treated with infliximab [32,33,34,35]. This may have led to less dose escalation, with Enbrel having lower annual TNFi costs, total RA-related medication costs, and total pharmacy costs [34,35].</p> <p>Psoriatic Arthritis (PsA) Enbrel’s use as a monotherapy for PsA has proven to be effective in controlling symptoms including improving physical functioning and reducing disease progression [36]. Moreover, Enbrel was deemed the most cost-effective</p>



Question	Sub-Question	Response
		<p>treatment option in PsA by the UK National Institute for Health Research (NIHR) [37].</p> <p>In PsA, Enbrel improves joint and skin symptoms while limiting joint damage, as well as improving physical functioning and the ability to perform daily activities [36,38,40]. In the PsA pivotal trial (Table 4), Enbrel significantly reduced signs and symptoms of PsA, reduced joint symptoms, improved psoriatic lesions, and inhibited radiographic progression [38]. ACR20 improvements were significantly greater in Enbrel compared to placebo (59% versus 15%) and were sustained at 24 and 48 weeks [38].</p> <p>Enbrel is the only TNFi to demonstrate clinical efficacy compared to MTX for PsA in a randomized clinical trial to date. In its largest ever randomized double-blind PsA clinical trial, Enbrel was compared directly to MTX (Table 4). This research provided high quality new evidence of Enbrel’s unique use in PsA, which is especially important for patients/providers with concerns about MTX tolerability and safety [36]. Compared to MTX monotherapy, Enbrel monotherapy produced greater ACR20 and minimal disease activity (MDA) response rates and had less radiographic progression at week 47 [36].</p> <p>Patients with PsA treated with Enbrel reported improvements in patient-reported outcomes (PROs). Enbrel’s improvement measured by the HAQ-DI was almost 10 times the improvement seen with placebo and was maintained for up to 2 years [40]. Additional PROs improvements from baseline were found with the SF-36, the EQ-5D visual analog scale (VAS), and the ACR patient pain assessment [40]. These commonly used measures encompass physical pain and functioning including social/emotional wellbeing. Almost half of patients treated with Enbrel reported no disability by the study’s end [40].</p> <p>Enbrel’s cost in treating PsA has been lower than common comparators including adalimumab monotherapy, ustekinumab 90 mg, secukinumab, and ixekizumab (data on file).</p> <p>Psoriasis (PsO)</p> <p>For patients with moderate to severe plaque psoriasis, Enbrel has been shown to help achieve clearer skin. In clinical trials (Table 5), PsO patients on Enbrel had a 66% mean Psoriasis Area and Severity Index (PASI) improvement at 12 weeks and 82% at 48 weeks, which was maintained through 120 weeks [39, 41]. PASI is a disease-specific measure of psoriasis severity across different body regions. Enbrel produces significant improvement in multiple PsO measures of skin signs and symptoms as well as the Dermatology Life Quality Index (DLQI). In the U.S. trial, significant PASI 75 response rates were observed at week 12 (34% for 25 mg BIW and 49% for 50 mg BIW) compared to placebo (4%, $p < 0.001$), and sustained through 24 weeks [41]. Additionally, long-term treatment (up to 72 weeks in open-label extension studies or up to 96 weeks with continuous 50 mg BIW) maintained significant improvements in PsO patients [42].</p> <p>The phase 3 studies of Enbrel in PsO (Table 5) demonstrated positive effects in PROs, including notable quality of life (QoL) improvements and reductions in fatigue levels, as compared to the placebo groups. A phase 3 study demonstrated an improvement in the Dermatology Life Quality Index of 47% to 61% in 12 weeks, compared to an 11% improvement in placebo ($P < .0001$) [43]. In a second study, greater proportions of Enbrel patients had at least</p>



Question	Sub-Question	Response
		<p>a 50% improvement in Hamilton Depression Rating Scale (HAM-D) or Beck Depression Inventory (BDI) at week 12 compared with placebo, as well as clinically meaningful improvements in fatigue, measured by mean functional assessment of chronic illness therapy fatigue (FACIT-F) [44].</p> <p>Further, Enbrel has been shown to have a lower actual-versus-expected dosing ratio and lower costs than ustekinumab. Administrative claims data have demonstrated that psoriasis patients with or without psoriatic arthritis who initiated treatment with Enbrel had a 20% lower actual-versus-expected dosing ratio while persistent on therapy and 25% lower total annual psoriasis-related costs than patients initiating ustekinumab [45].</p> <p>Safety – PsA/PsO</p> <p>Enbrel’s safety profile in PsA and PsO is robust and similar to that of RA. In the PsA pivotal trial, Enbrel was well tolerated [38]. A lower rate of withdrawals due to adverse reactions has been reported with Enbrel compared to infliximab in PsA [46]. In PsO, only 2% of patients discontinued due to side effects at 120 weeks [39]. See Table 7 for additional safety data across Enbrel’s indications.</p> <p>Ankylosing Spondylitis (AS)</p> <p>Enbrel controls TNF-mediated joint inflammation in patients with AS, improving signs, symptoms, and PROs. Consistent and sustained Assessment in Spondylarthritis International Society (ASAS) defined clinical response was observed with long term treatment over 3 years in patients with axial spondyloarthritis [47]. Imaging data indicated that there was no increase of fatty lesions, a marker of future structural damage, during continuous treatment with Enbrel, and only a very low rate of new-onset osteitis was found during the 3 years of treatment [48]. In patients with nonradiographic axial spondyloarthritis, Enbrel treatment was associated with rapid, significant improvement in symptomatic disease activity, function, and systemic and skeletal inflammation [49]. Clinical and functional improvements were sustained up to 24 and 48 weeks following 12 weeks of treatment, and PROs also improved [49].</p> <p>Current Costs (Table 6)</p> <p>As with all manufacturers, Amgen has worked with pharmacy benefit managers (PBMs) and insurers to ensure patients have access to Enbrel. This has resulted in discounting of the drug to these entities. Based on SSR data, Enbrel has one of the highest discounts across b/ts DMARDs. This can help Enbrel patients to remain on the drug they have found to be effective.</p>
	<p>Hyperlink to Citation - Additional Materials for Question 28</p>	



Question	Sub-Question	Response
	Hyperlink to Table/Charts/Graphs - Additional Materials for Question 28	
	Evidence Submitted include a cost-effectiveness measure?	Y
	What type of Evidence is shown?	N
Question 29: Comparative Effectiveness on Specific Populations	Response to Question 29	<p>Evidence includes cost per effectively treated patient.</p> <p>The evidence referenced in this section ranges from 2000 to 2022.</p> <p>Medicare Populations Enbrel has been shown to have the lowest cost per effectively treated patient versus its closest therapeutic alternatives, using a validated “effectiveness” algorithm of 6 criteria representing high adherence, no increase in biologic dose or frequency, no biologic switch, no new DMARD, no new chronic oral glucocorticoid or dose increase, and limited multiple joint injections [1]. Applying these criteria to real-world data has shown Enbrel to have a lower cost per effectively treated patient [2].</p> <p>RA Medicare-aged patients were included in several of Enbrel’s short- and long-term clinical trials, including those demonstrating ACR improvements, reduced radiographic progression, reduced injection site pain, fewer adverse reactions than MTX, and higher rates of remission (defined by SDAI score ≤ 3.3) compared to MTX [3,4,5,6]. Age stratified post-hoc analysis has also shown that Enbrel’s sustained functional improvements as measured by HAQ-DI in the RA 65+ population are similar to those seen in younger populations [7,8].</p> <p>Enbrel delivers value to Medicare patients with 1) a greater number of “effectively” treated patients and 2) the</p>



Question	Sub-Question	Response
		<p>lowest 1-year cost per effectively treated patient compared to adalimumab, infliximab, and abatacept. In a claims analysis of 14,244 Medicare beneficiaries with moderate to severe RA, a greater proportion of Enbrel patients were “effectively” treated compared to adalimumab, infliximab, and abatacept [2]. “Effectiveness” in this study applied a validated algorithm using claims data to identify low disease activity or remission. To determine if a patient’s treatment was “effective,” the algorithm used six criteria: high adherence, no increase in biologic dose or frequency, no biologic switch, no new DMARD, no new chronic oral glucocorticoid or dose increase, and limited multiple joint injections [1,2]. The analysis classified medications as 26% “effective” for abatacept, 24% for adalimumab, 28% for Enbrel and 23% for infliximab and mean cost per effectively treated patient was \$55,096 for abatacept, \$51,4436 for adalimumab, \$45,910 for Enbrel and \$62,666 for infliximab. Enbrel offers valuable benefits to Medicare patients compared to other therapeutic alternatives for managing RA. In addition, the same analysis found that among disabled Medicare patients, Enbrel had greater “effectiveness” (measured by the algorithm described above) compared to infliximab. In this claims analysis, Medicare patients with disability were reported to have experienced 48% greater “effectiveness” with Enbrel treatment versus infliximab [2].</p> <p>RA is especially burdensome for older patients, and Enbrel has consistent benefits across all age groups. The likelihood of developing RA increases with age, and the onset of RA is highest among adults in their sixties [9]. Evidence indicates that patients over the age of 65 with either early or late RA tend to have worse baseline disability as measured by HAQ-DI and increased RA-associated mortality, illustrating greater need for treatment [7,10]. A recent analysis in the U.S. Medicare population has noted that RA patients have a significantly greater comorbidity burden and healthcare resource utilization, with all-cause healthcare costs being 3-fold higher (driven mainly by higher outpatient costs) than non-RA Medicare patients [11]. This evidence demonstrates persistent unmet need in the Medicare population, and the need for a coverage environment that incentivizes utilization of effective biologics like Enbrel. In this older patient population, Enbrel led to rapid improvements in HAQ-DI within the first 3 months of treatment initiation, which were sustained through 6 years of therapy and consistent with results observed in younger patients [7]. Other studies have confirmed similar efficacy and QoL benefits regardless of age [12,13].</p> <p>Older Patients, Racial & Ethnic Populations</p> <p>Considering RA’s increased incidence in women, racial trends in comorbidities, and the role of socioeconomic status in disease outcomes and healthcare access, Enbrel plays a vital role in reducing disparities and improving health equity in RA management.</p> <p>Socioeconomic disparities in morbidity, mortality, access to care, and quality of care have been widely recognized as pressing health equity concerns, and RA is not exempt. Its incidence is far greater in women than men (53.1/100,000 population versus 27.7/100,000 population), the prevalence of comorbidities are higher in certain races, and race and socioeconomic status are correlated with RA-related disability [14,15]. Access to treatment is also a concern; an analysis of 93,143 Medicare patients with RA found significant disparities in treatment patterns, with African American race and low-income level being associated with a lower likelihood of treatment with DMARDs [16].</p>



Question	Sub-Question	Response
		<p>Cardiovascular disease is a leading cause of death in RA patients: this risk increases in older patients and even more so in older African American patients. Older RA patients have an increased atherosclerotic cardiovascular disease (ASCVD) risk compared to younger patients and African Americans with RA have an increased risk for ASCVD compared to white Americans with RA. In a study of 287,467 adults, ASCVD risk in African Americans with RA was 37.4% versus 20.5% in white adults [17]. RA-related autoantibodies remain an independent risk factor in subclinical atherosclerosis and ensuing cardiovascular events. This has been observed even in patients without an RA diagnosis who have RA-related autoantibodies, with African American women at greater risk of cardiovascular events as shown in the Multi-Ethnic Study of Atherosclerosis (MESA) [18]. In addition, the results from the Oral Rheumatoid Arthritis Trial (ORAL) Surveillance found that in 1,455 patients receiving the JAKi tofacitinib and 1,451 patients 50 years or older receiving a TNFi, incidences of major adverse cardiovascular events (MACE) and cancer were higher in the patients receiving tofacitinib [19]. RA disease control is a cornerstone of decreasing cardiovascular disease [20]. Enbrel combination therapy has a favorable benefit-risk profile for Latinx patients. An open-label, active comparator study in Latin American populations has shown the addition of Enbrel to MTX to be more efficacious for treating RA than adding another conventional DMARD, with no new safety issues [21].</p> <p>Enbrel provides an option to RA patients who are at greater risk of herpes zoster (HZ) compared to JAK inhibitors. The risk of HZ rises in patients who have RA and can be further impacted by age, ethnicity, diabetes, and smoking [22,23]. JAK inhibitors have an increased risk of herpes zoster (HZ) compared to biologics [24]. TNFis have demonstrated no heightened risk of HZ versus conventional synthetic DMARDs, however, opportunistic infections, including atypical mycobacterial infection, herpes zoster, aspergillosis and Pneumocystis jiroveci pneumonia, and protozoal infections have also been reported in postmarketing use [35]. Medicare and MarketScan data have shown that patients initiating the JAKi tofacitinib for RA had a crude HZ incidence rate of 3.87 (2.82, 5.32); for biologic DMARDs, the crude incidence rate (95% CI) was at most 2.71 (2.33, 3.08; infliximab). In tofacitinib clinical trials, incidence was 3.9 for tofacitinib and 3.2 for baricitinib. For both treatments, incidence rates were higher in Asian countries [24].</p> <p>Patients with Psychiatric Comorbidities</p> <p>For patients with moderate to severe psoriasis, Enbrel not only improves psoriasis area and severity index (PASI) scores and reduces visible symptoms but also offers potential benefits in addressing psychiatric comorbidities. Enbrel's clinical impact in improving depressive symptoms, supported by longer-term outcomes, highlights its potential value in addressing mental health challenges faced by PsO patients.</p> <p>By improving PASI scores and reducing the visibility of plaque psoriasis, Enbrel can potentially benefit PsO patients suffering from comorbid mental health challenges. PsO is linked to numerous psychiatric conditions, including anxiety, depression, and schizophrenia [25]. Highly visible PsO symptoms contribute to and are exacerbated by psychosocial stress (low-self-esteem, social isolation, etc.), while discomfort from itch, joint inflammation, and pain compromise health-related QoL [25, 26]. Higher PASI scores have been found to be correlated with depression, suggesting Enbrel's clinical impact can facilitate improvement in psychiatric comorbidities [27]. This was supported</p>



Question	Sub-Question	Response
		<p>by longer-term outcomes from Enbrel’s 12-week randomized PsO trial, which measured depression symptoms using HAM-D and BDI scales for depression [28]. Mean scores for both were improved with Enbrel and there was a greater proportion of responders (≥50% improvement from baseline) at week 12 of the double-blind period; these advances were sustained through week 96 [28].</p> <p>Pediatric Patients</p> <p>As the only biologic indicated for PsO patients as young as 4 years old by the FDA, Enbrel effectively reduces lesion severity improving PASI 75 and PASI 90 responses [29]. Decades of clinical use and evaluation in juvenile idiopathic arthritis confirm Enbrel’s safety, efficacy, and tolerability profile in pediatric patients.</p> <p>Amgen continues to reinvest in Enbrel to expand its benefits to as many patients as possible, including pediatric PsO patients. Enbrel is one of 4 biologics indicated by the FDA for pediatric patients with moderate-to-severe plaque PsO, and it is the only FDA-approved biologic for patients as young as 4 years old [30]. Enbrel’s safety and efficacy in pediatric patients with moderate to severe PsO have been evaluated in a phase 3 study, followed by a 5-year open-label extension, and post-marketing study [29,31,32,33,34]. In this population, Enbrel effectively reduces the severity of lesions and the skin area involved, and it improves PASI 75 and PASI 90 responses compared with placebo [29]. The adverse reaction profile was generally similar to adult patients with moderate to severe plaque PsO, and PASI 75 and 90 response was maintained through week 36. No post-marketing risk evaluation or mitigation strategies have been required.</p>
	<p>Hyperlink to Citation - Additional Materials for Question 29</p>	<p>[REDACTED]</p>
	<p>Hyperlink to Table/Charts/Graphs - Additional Materials for Question 29</p>	<p>[REDACTED]</p>



Question	Sub-Question	Response
	Evidence Submitted include a cost-effectiveness measure?	Y
	What type of Evidence is shown?	N
Question 30: Addressing Unmet Medical Needs	Response to Question 30	<p>The evidence referenced in this section ranges from 2008 to 2022.</p> <p>Unmet Need</p> <p>Enbrel revolutionized patient care for those with moderate to severe RA by introducing a groundbreaking and innovative treatment solution. As the first FDA-approved TNFi agent, Enbrel rapidly slowed disease activity and physical decline, expanding the possibility of remission to a broader scope of RA sufferers while extending its utility to diseases like PsO and PsA. Continuous investment in research and development has resulted in its use in other diseases, multiplying the number of lives improved. Enbrel’s unique benefits emphasize the importance for a diverse set of treatment options in the complex landscape of inflammatory disease, warranting broad coverage by payers. For decades, the outlook for RA patients was grim. Gold and NSAIDs were dominant treatments but failed to prevent progression and brought along gruesome complications, including gastrointestinal bleeding, nephrotoxicity, rashes, and nausea [1]. Under these treatment conditions, patients spiraled into disability and struggled to hold jobs, remain in school, or complete daily tasks because their joints were so painfully inflamed and eroded [1]. As stated by Amgen CEO, Robert A. Bradway, “Physicians who treat patients with autoimmune disorders like moderate to severe rheumatoid arthritis remind us that their waiting rooms used to be cluttered with canes, crutches, and wheelchairs – even stretchers. That’s how debilitating untreated moderate-to-severe rheumatoid arthritis can be. That is no longer the case due to the introduction of innovative medicines like Enbrel [2].”</p> <p>Remembering this not-too-distant reality sheds light on the true value of innovation in the rheumatology space. Even in the early 1990s, a number DMARDs, while somewhat palliative for symptoms, were sparsely effective in improving structural outcomes [3]. MTX’s status as a preferred treatment was shadowed by intolerability, inadequate responses, and contraindications for large patient sectors [3]. As the first ever TNFi agent approved by the FDA in 1998, Enbrel represented a ground-breaking shift in the treatment landscape [3]. Finally, rapid slowing of disease activity and physical decline were possible in tolerable doses, expanding the possibility of remission to a broader group of RA sufferers. Through continuous investment in research and development, Enbrel’s utility has suffused to diseases with similar pathophysiology like PsA and PsO, improving patients’ lives.</p> <p>As exemplified by RA advancements in the 20th century, the complexity of inflammatory diseases necessitates constant innovation and a variety of treatment options. Despite the preponderance of therapeutics in RA, PsA, and</p>



Question	Sub-Question	Response
		<p>PsO, significant unmet need persists. There are no cures for these conditions, and many patients must try and fail on multiple treatments before finding what works for them. For this reason, it is important to have a variety of therapeutic options available, while continuously investigating opportunities to enhance efficacy, safety, and convenience for patients. Since its launch, Enbrel has remained a cornerstone of care, offering relief from pain, preventing joint damage, and vastly improving QoL for patients [4,5]. Managing an inflammatory condition can be complex - each patient has a different response to therapy, and for this reason, Enbrel continues to hold a critical place in patient care that is irreplaceable [2].</p> <p>Enbrel’s safety, maintenance of remission, low rate of immunogenicity, and low rates of switching distinguish it from comparators and confirm its utility in the RA, PsA, and PsO markets. Enbrel’s ability to maintain remission itself can reduce medical costs (in-patient and outpatient visits, etc.) in RA [6,7,8]. In addition, many other TNFi are associated with secondary failure and adverse reactions that may be associated with the development of anti-drug antibodies in RA [9]. Enbrel has been shown to be the least immunogenic TNFi, with no known development of neutralizing antibodies [9,10]. This may allow for more stable dosing, which is associated with lower costs and potentially fewer side effects underscored by evidence indicating notably elevated hazard rates for bDMARDs in cases of dose escalation when contrasted with non-escalators [11,12,13,14,15,16,17]. Enbrel’s low rate of immunogenicity may also reduce the need for methotrexate co-administration (used to counteract the formation of anti-drug antibodies) [6,18]. Enbrel’s lower rates of biologic switching compared to adalimumab and infliximab may also be related to its low immunogenicity, since the formation of neutralizing anti-drug antibodies in infliximab and adalimumab can lead to diminished effectiveness [9,19]. Lower rates of switching in turn lead to lower treatment costs, again distinguishing Enbrel from its comparators [19]. Treatment failure and switching is a common challenge in rheumatoid arthritis. An analysis of median treatment duration in 2018-2021 observed that patients taking 3 or more lines of therapy remained on first, second, and third line therapies for only 153, 108, and 117 days, respectively [20].</p> <p>In summary, inflammatory disease manifestations and outcomes are inherently heterogenous, leading to persistent unmet need. Innovative medicines like Enbrel have given patients new hope for the possibility of a longer, higher-quality life. In a landscape where one size does not fit all, each treatment has unique benefits, making it imperative that reimbursement structures appropriately value the nuanced advantages of Enbrel.</p>
	<p>Hyperlink to Citation - Additional Materials for Question 30</p>	<p>[REDACTED]</p>



Question	Sub-Question	Response
	Hyperlink to Table/Charts/Graphs - Additional Materials for Question 30	[REDACTED]
	Evidence Submitted include a cost-effectiveness measure?	N
	What type of Evidence is shown?	
Question 31: Patient and Caregiver Experience	Response to Question 31	
Question 32: Executive Summary	Response to Question 32	<p>The introduction of Enbrel effectively redefined the clinical course of RA. Many patients who previously would have endured progressive and painful deformities and immobility now live for years or decades with lower pain, less progression, and greater function. Since then, Enbrel has been approved in 4 more disease areas, many of which affect the elderly, owing to the broad utility of TNF inhibition in transforming the clinical course of many inflammatory diseases.</p> <p>Across RA, PsA, and PsO, Enbrel has demonstrated clinically meaningful improvements in outcomes such as reductions in joint pain and damage, improved physical functioning, and reduction in skin-related symptoms. Enbrel is effective for long-term control of disease and has demonstrated these benefits in head-to-head as well as standalone studies. For example, Enbrel monotherapy in RA has shown greater efficacy than methotrexate monotherapy, the previous standard treatment, in achieving ACR criteria, LDA response, and reduced radiographic progression. Looking at head-to-head performance in PsA, combining methotrexate with Enbrel did not improve Enbrel efficacy, distinguishing the TNF pathway as uniquely important and Enbrel as an effective monotherapy. In</p>



Question	Sub-Question	Response
		<p>PsO, where safety of systemic treatments is particularly important in the risk-benefit calculation, Enbrel improves multiple measures of skin signs and symptoms as well as a number of PRO measures. Improvements in disease activity and PROs with Enbrel were maintained long-term (up to 96 weeks). Finally, looking at Enbrel compared with other TNF agents and non-TNF systemic therapies, numerous claims analyses using a validated algorithm have consistently shown Enbrel to have the highest proportion of “effectively” treated patients compared to adalimumab and infliximab. This has been confirmed in three NMAs in RA, helping to differentiate Enbrel from other biologics. Enbrel achieves disease transforming efficacy while also offering an established safety profile. In RA, Enbrel patients experience fewer adverse reactions, including infections, compared to those on MTX. Enbrel may also require less MTX supplementation than other biologics, which could reduce the additional side effects. Real-world evidence has shown Enbrel to have fewer adverse reactions than infliximab and adalimumab as well, with Enbrel patients having higher adherence as a result. Finally, Enbrel improves PROs and productivity in adults with RA, PsA, and PsO, boosting patient wellbeing and reducing costs for employers.</p> <p>In RA, switching to Enbrel after failure of another TNFi has been shown to improve ACR response, which is an important finding for both physicians and patients. Because TNF-treated inflammatory conditions are chronic and no cure exists, physicians and patients need access to multiple therapeutics to sustain response and remission over the course of a patient’s lifetime, highlighting the importance of broadening the availability of Enbrel to patients of different ages who need to switch off a less effective or less tolerable therapeutic alternative, including alternative TNFis.</p> <p>Amgen’s investments in Enbrel have improved the patient experience regarding pain and discomfort with injections, a common concern amongst patients on lifelong treatments. A phosphate-free formulation of Enbrel has shown to have lower injection site pain, and innovative autoinjector designs make self-administration more comfortable and convenient, especially for patients with dexterity limitations or disabilities.</p> <p>In numerous studies involving diverse sets of commercial and Medicare patients, Enbrel has shown to be the most cost-effective treatment with the lowest 1-year cost per effectively treated patient compared to adalimumab, infliximab, and abatacept. Enbrel is the only human soluble receptor TNFi and effectively treats RA, PsA, PsO, and AS by reducing disease activity and symptoms in balance with side effects and patient ability to maintain adherence and dosing. In a comparison with adalimumab, infliximab, and abatacept, Enbrel has demonstrated a greater proportion of “effectively” treated RA patients, underscoring that Enbrel is a choice that should be readily available to all patients when options for effective disease management are considered.</p> <p>Analysis of treatment practice patterns across multiple databases has shown Enbrel to have the lowest dose escalation rates among TNFis. Unlike other TNFis, Enbrel’s labeling does not specify dose escalation; its reduced likelihood of dose escalation is associated with lower healthcare costs and potentially less dose-related toxicity for patients. Relatedly, Enbrel has not been shown to develop neutralizing anti-drug antibodies that can compromise efficacy and necessitate treatment switching.</p> <p>Enbrel is a valuable treatment option for older patients, those with psychiatric comorbidities, Latinx populations,</p>



Question	Sub-Question	Response
		<p>and pediatric psoriasis patients. Enbrel is an effective treatment option in the 65+ population, where RA diagnosis is associated with significantly worse comorbidities, increased healthcare resource utilization, and higher costs. Additionally, Enbrel’s ability to clear symptoms, improve QoL, and maintain remission holds secondary utility for patients suffering from comorbid mental health conditions. Enbrel also is one of the few biologics available for pediatric psoriasis patients.</p> <p>Overall, Enbrel’s unique qualities can meet unmet clinical and economic needs as initial treatment for many inflammatory diseases. Enbrel is also an effective successor treatment when other treatments (including other TNFs) lose effectiveness, are less well tolerated, or require undesired dose intensification. Its low immunogenicity, established safety, and low dose escalation have given Enbrel a singular role among TNFis, and it continues to fill critical gaps in the RA, PsA, and PsO treatment landscapes. Because a majority of Medicare beneficiaries on Enbrel are long-time patients who have found stability and relief from Enbrel, it is essential to protect access for these patients.</p>

Table 1. Key Enbrel Clinical Studies in Patients with Moderate-to-Severe Rheumatoid Arthritis

Description	Study Arms	Key Results	Publications
<ul style="list-style-type: none"> • Placebo-controlled • cDMARD refractory • n = 234 • Mean disease duration 11 to 13 years 	<ul style="list-style-type: none"> • ETN 10 mg BIW* • ETN 25 mg BIW • Placebo 	<p>Clinical</p> <ul style="list-style-type: none"> • At 3 months, proportion of patients achieving ACR20 <ul style="list-style-type: none"> – 62% in the ETN 25 mg group (p < 0.001) – 45% in the ETN 10 mg group (p = 0.003) – 23% in the placebo group • At 3 months, proportion of patients achieving ACR50 <ul style="list-style-type: none"> – 41% in the ETN 25 mg group (p < 0.001) – 13% in the ETN 10 mg group (p > 0.2) – 8% in the placebo group • At 6 months, proportion of patients achieving ACR20 <ul style="list-style-type: none"> – 59% in the ETN 25 mg group (p < 0.001) – 51% in the ETN 10 mg group (p < 0.001) – 11% in the placebo group • At 6 months, proportion of patients achieving ACR50 <ul style="list-style-type: none"> – 40% in the ETN 25 mg group (p < 0.001) – 24% in the ETN 10 mg group (p < 0.001) – 5% in the placebo group <p>Functional</p> <ul style="list-style-type: none"> • All components of HAQ improved over baseline in both ETN groups at 3 and 6 months compared with placebo 	<p>Moreland, Larry W., et al. "Etanercept Therapy in Rheumatoid Arthritis". <i>Annals of Internal Medicine</i>, vol 130, no. 6, 1999, pp. 44778-4486. Available from: https://www.acpjournals.org/doi/pdf/10.7326/0003-4819-130-6-199903160-00004</p>
<ul style="list-style-type: none"> • Combination MTX study • MTX refractory • n = 89 • Mean disease duration 13 years 	<ul style="list-style-type: none"> • ETN 25 mg BIW + MTX • MTX 	<p>Clinical</p> <ul style="list-style-type: none"> • At 24 weeks, proportion of patients achieving ACR20 <ul style="list-style-type: none"> – 71% in the ETN + MTX group (p < 0.001) – 27% in the MTX group <p>Functional</p> <ul style="list-style-type: none"> • At 12 and 24 weeks, median HAQ disability-index score improved with ETN + MTX over MTX monotherapy (p ≤ 0.006) 	<p>Weinblatt, Michael E., et al. "A Trial of Etanercept, a Recombinant Tumor Necrosis Factor Receptor: Fc Fusion Protein, in Patients with RA receiving MTX." <i>N Engl J Med</i>, vol 3440, 1999, pp. 253-259. Available from: https://www.nejm.org/doi/full/10.1056/nejm199901283400401</p>

Description	Study Arms	Key Results	Publications
<ul style="list-style-type: none"> • TEMPO • cDMARD refractory other than MTX • n = 682 • Mean disease duration 6.3 to 6.8 years 	<ul style="list-style-type: none"> • ETN 25 mg BIW + MTX • ETN 25 mg BIW • MTX 	<p>Clinical</p> <ul style="list-style-type: none"> • At 24 weeks, proportion of patients achieving ACR-N AUC <ul style="list-style-type: none"> – 18.3%-years in the ETN + MTX group (p < 0.0001) – 14.7%-years in the ETN group (p = 0.0034) – 12.2%-years in the MTX group <p>Radiographic</p> <ul style="list-style-type: none"> • At 52 weeks, change from baseline mean TSS <ul style="list-style-type: none"> – 0.54 in the ETN + MTX group (p < 0.0001) – 0.52 in the ETN group (p = 0.0469) – 2.80 in the MTX group <p>Functional</p> <ul style="list-style-type: none"> • At 1 year, mean HAQ disability-index score improved with ETN + MTX over MTX or ETN monotherapy (p < 0.0001) 	<p>Klareskog, Lars et al. "Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomized controlled trial." <i>Lancet</i>, vol 363, no. 9410, 2004, pp. 675-81. Available from: https://pubmed.ncbi.nlm.nih.gov/15001324/</p> <p>Van der Heijde, Desiree et al. "Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: Two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial." <i>Arthritis Rheum</i>. Vol 54, no. 4, 2006, pp. 1063-74. Available from: https://pubmed.ncbi.nlm.nih.gov/16572441/</p> <p>Van der Heijde, Desiree et al. "Disease remission and sustained halting of radiographic progression with combination etanercept and methotrexate in patients with rheumatoid arthritis." <i>Arthritis Rheum</i>. Vol 56, no. 12, 2007, pp. 3928-39. Available from: https://pubmed.ncbi.nlm.nih.gov/18050208/</p>
<ul style="list-style-type: none"> • ERA study • ERA ≤ 3 years • n = 632 • Mean disease duration 11 to 12 months 	<ul style="list-style-type: none"> • ETN 10 mg BIW* • ETN 25 mg BIW • MTX 	<p>Clinical</p> <ul style="list-style-type: none"> • At 3, 6, 9, and 12 months, proportion of patients achieving ACR-N <ul style="list-style-type: none"> – Significantly greater areas under the curve for ETN 25-mg group than for MTX group (p < 0.05) <p>Radiographic</p> <ul style="list-style-type: none"> • At 6 months, change from baseline mean TSS <ul style="list-style-type: none"> – 0.57 in the ETN 25-mg BIW group (p = 0.001) – 1.06 in the MTX group 	<p>Bathon, Joan M et al. "A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis." <i>New Engl J Med</i>, vol 343, 2000, pp. 1586-1593. Available from: https://www.nejm.org/doi/10.1056/NEJM200011303432201?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%20www.ncbi.nlm.nih.gov</p> <p>Genovese, Mark C et al. "Etanercept Versus Methotrexate In Patients With Early Rheumatoid Arthritis: Two-Year Radiographic And Clinical Outcomes." <i>Arthritis & Rheum</i>, vol 46, no 6, 2002, pp1443-1450. Available from: https://onlinelibrary.wiley.com/doi/pdf/10.1002/art.10308</p>

Description	Study Arms	Key Results	Publications
<ul style="list-style-type: none"> • COMET • ERA 3 to 24 months • N=542 • Mean (SD) disease duration 9.0 (0.3) months 	<ul style="list-style-type: none"> • ETN 50mg QW + MTX • MTX 	<p>Clinical</p> <ul style="list-style-type: none"> • At 52 weeks, proportion of patients achieving DAS28 < 2.6 <ul style="list-style-type: none"> – 50% in the ETN 50 mg QW + MTX group (p <0.0001) – 28% in the MTX group <p>Radiographic</p> <ul style="list-style-type: none"> • At 52 weeks, proportion of patients achieving mean mTSS ≤ 0.5 <ul style="list-style-type: none"> – 80% in the ETN 50 mg QW + MTX group (p <0.0001) – 59% in the MTX group • At week 52, proportion of patients difference of 0.22 in HAQ score <ul style="list-style-type: none"> – 88% in the ETN 50 mg QW + MTX group (p <0.006) – 78% in the MTX group <p>Functional</p> <ul style="list-style-type: none"> • At 1 year, mean HAQ disability-index score improved with ETN + MTX over MTX monotherapy (p <0.0001) 	<p>Emery, Paul et al. "Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial." <i>Lancet</i>, vol 372, no. 9636, 2008, pp. 375-82. Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(08)61000-4/fulltext</p> <p>Kekow, Jörn et al. "Patient-reported outcomes improve with etanercept plus methotrexate in active early rheumatoid arthritis and the improvement is strongly associated with remission: the COMET trial." <i>Annals of the Rheumatic Diseases</i>, vol 70, 2011, pp.1519. Available from: https://ard.bmj.com/content/69/01/222.long</p> <p>Emery, Paul et al. "Combination etanercept and methotrexate provides better disease control in very early (<=4 months) versus early rheumatoid arthritis (>4 months and <2 years): post hoc analyses from the COMET study" <i>Ann Rheum Dis</i>, vol 71, 2012, pp.989-992. Available from: https://pubmed.ncbi.nlm.nih.gov/22402142/</p> <p>Emery, Paul et al. "Two-year clinical and radiographic results with combination etanercept-methotrexate therapy versus monotherapy in early rheumatoid arthritis: a two-year, double-blind, randomized study." <i>Arthritis Rheum</i>, vol 62, 2010, no. 3, pp. 674-82. Available from: https://pubmed.ncbi.nlm.nih.gov/20187135/</p> <p>Dougados, Maxime R et al. "When to adjust therapy in patients with rheumatoid arthritis after initiation of etanercept plus methotrexate or methotrexate alone: findings from a randomized study (COMET)." <i>J Rheumatol</i>, vol 41, 2014, no. 10, pp. 1922-34. Available from: https://pubmed.ncbi.nlm.nih.gov/25128520/</p>

ACR-N AUC = American College of Rheumatology numeric index of the ACR response area under the curve; BIW = twice weekly; DAS28 = Disease Activity Score in 28 joints; DMARD = disease-modifying antirheumatic drug; ETN = etanercept; ERA = early rheumatoid arthritis; mTSS = modified total Sharp score; HAQ = Health Assessment Questionnaire; MTX = methotrexate; PROs = patient-reported outcomes; QW = once weekly; RA = rheumatoid arthritis; TEMPO = Trial for Etanercept and Methotrexate With Radiographic Patient Outcomes.

*not an FDA-approved dosage

Table 2. NMA Derived Proportions of Patients in Each ACR Non-overlapping Response Category, by Targeted Immune Modulator Combination Regimen: Mixed Population [10]

Treatment	ACR<20	ACR 20-50	ACR 50-70	ACR 70-100
Etanercept + cDMARD	29%	23%	21%	27%
Certolizumab pegol + cDMARD	29%	23%	21%	26%
Tocilizumab (iv) + cDMARD	38%	23%	19%	19%
Sarilumab + cDMARD	40%	23%	19%	18%
Golimumab (sc) + cDMARD	41%	23%	18%	17%
Abatacept (iv) + cDMARD	42%	23%	18%	17%
Golimumab (iv) + cDMARD	42%	23%	18%	17%
Baricitinib + cDMARD	42%	23%	18%	16%
Tocilizumab (sc) + cDMARD	43%	23%	18%	16%
Abatacept (sc) + cDMARD	43%	23%	18%	16%
Infliximab + cDMARD	45%	23%	17%	15%
Adalimumab + cDMARD	45%	23%	17%	15%
Tofacitinib + cDMARD	47%	23%	17%	14%
Rituximab + cDMARD	48%	23%	16%	13%
Intensive cDMARD	50%	23%	16%	12%
Conventional DMARD	73%	16%	8%	4%

Bolded = TNFis

Table 3. NMA Derived Proportions of Patients in Each ACR Non-overlapping Response Category, by Targeted Immune Modulator Monotherapy Regimen: Mixed Population [10]

Treatment	ACR<20	ACR 20-50	ACR 50-70	ACR 70-100
Tocilizumab (iv)	25%	24%	21%	30%
Etanercept	27%	24%	20%	28%
Sarilumab	28%	25%	20%	27%
Adalimumab	43%	25%	16%	16%
Conventional DMARD 70%	70%	18%	8%	4%

Bolded = TNFis

Table 4. Key Clinical Studies in Patients with Psoriatic Arthritis

Description	Study Arms	Key Results	Publications
<ul style="list-style-type: none"> Patients with PsO and PsA N = 60 	<ul style="list-style-type: none"> ETN 25 mg BIW Placebo 	<ul style="list-style-type: none"> At week 12, proportion of patients achieving PsARC <ul style="list-style-type: none"> 87% in the ETN group (p < 0.0001) 4% in the placebo group At week 12, proportion of patients achieving ACR 20 <ul style="list-style-type: none"> 73% in ETN group (p < 0.0001) 13% in the placebo group At 12 weeks, median improvement in PASI score <ul style="list-style-type: none"> 46% in the ETN group (p = 0.0032) 9% in the placebo group 	<p>Mease, Phillip J., et al. "Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomized trial." <i>Lancet</i>, vol 356, 2000, pp. 385-390. Available from: https://pubmed.ncbi.nlm.nih.gov/10972371/</p>
<ul style="list-style-type: none"> Patients with PsO and PsA N = 205 	<ul style="list-style-type: none"> ETN 25 mg BIW Placebo 	<ul style="list-style-type: none"> At week 12, proportion of patients achieving ACR20 <ul style="list-style-type: none"> 59% in the ETN group (p < 0.0001) 15% in the placebo group At 12 months, mean mTSS change from baseline <ul style="list-style-type: none"> - 0.03 in ETN group (p = 0.0001) 1.00 in placebo group Annualized changes in the erosion score and JSN also were significantly different between groups At 2 years (n = 169 for open-label), proportion of patients achieving ACR20, PsARC, PASI 50 <ul style="list-style-type: none"> 64%, 84%, 62% in the ETN/ETN group respectively 63%, 80%, 73% in the placebo/ETN group respectively At 2 years, mean adjusted TSS change from baseline <ul style="list-style-type: none"> -0.38 in the ETN/ETN group respectively 0.50 in the placebo/ETN group (0.72 baseline to year 1 	<p>Mease, Philip J., et al. "Etanercept Treatment of Psoriatic Arthritis: Safety, Efficacy, and Effect on Disease Progression. <i>Arthritis & Rheumatism</i>, vol. 50, no. 7, 2004, pp. 2264-2272. Available from: https://doi.org/10.1002/art.20335</p> <p>Mease, Phillip J., et al. "Continued inhibition of radiographic progression in patients with psoriatic arthritis following 2 years of treatment with etanercept." <i>J Rheumatol</i>, vol 33, 2006, pp. 712-721. Available from: https://pubmed.ncbi.nlm.nih.gov/16463435/</p>

[placebo] then -0.22 year to year 2 [ETN]			
Description	Study Arms	Key Results	Publications
<ul style="list-style-type: none"> • Biologic- and MTX-naïve patients with PsA • N = 851 	<ul style="list-style-type: none"> • ETN 50 mg QW + MTX 20 mg QW • ETN 50 mg QW • MTX 20 mg QW 	<ul style="list-style-type: none"> • At week 24, proportion of patients achieving ACR20 response <ul style="list-style-type: none"> – 60.9% for ETN monotherapy vs 50.7% for MTX monotherapy (adjusted p = 0.029) – 65.0% for ETN + MTX combination vs 50.7% for MTX monotherapy (adjusted p = 0.005) • At week 24, proportion of patients achieving MDA response <ul style="list-style-type: none"> – 35.9% for ETN monotherapy vs 22.9% for MTX monotherapy (adjusted p = 0.005) – 35.7% ETN + MTX combination vs 22.9% for MTX monotherapy (adjusted p = 0.005) 	<p>Mease, Philip J., et al. "Etanercept and Methotrexate as Monotherapy or in Combination for Psoriatic Arthritis: Primary Results From a Randomized, Controlled Phase III Trial." <i>Arthritis & Rheumatology</i>, vol. 71, no. 7, 2019, pp. 1112-1124. Available from: https://doi.org/10.1002/art.40851</p>

ACR = American College of Rheumatology, BIW = twice weekly; ETN = etanercept; JSN = joint spacing narrowing; mTSS = modified Total Sharp Score; PsA = Psoriatic arthritis; PsARC = Psoriatic arthritis response criteria; PASI = Psoriasis Area and Severity Index; PsO = Psoriasis

*not an FDA-approved dosage

Table 5. Key Clinical Studies in Patients with Psoriasis

Description	Study Arms	Key Results	Publications
<ul style="list-style-type: none"> US phase 3 (part 1) 24-week study N = 672 	<ul style="list-style-type: none"> ETN 50 mg BIW ETN 25 mg BIW ETN 25 mg QW* Placebo 	<ul style="list-style-type: none"> At week 12, proportion of patients achieving PASI 75 <ul style="list-style-type: none"> 49% in the ETN 50-mg BIW group (p < 0.001) 34% in the ETN 25-mg BIW group (p < 0.001) 14% in the ETN 25-mg QW group (p < 0.001) 4% in the placebo group 	<p>Leonardi, Craig L., et al. "Etanercept as monotherapy in patients with psoriasis" <i>N Engl J Med</i>, vol 349, 2014, pp. 22. Available from: https://pubmed.ncbi.nlm.nih.gov/14627786/</p>
<ul style="list-style-type: none"> US phase 3 (part 2) Responders discontinued ETN until relapse then reinitiated ETN Entered the study drug discontinuation period (n = 409); relapsed and entered the retreatment period (n = 347) Completed 12 weeks of retreatment n = 297 	<ul style="list-style-type: none"> ETN 50 mg BIW ETN 25 mg BIW ETN 25 mg QW* Placebo/ETN 25 mg BIW* 	<ul style="list-style-type: none"> At 12 weeks of retreatment, proportion of patients achieving PASI 75 <ul style="list-style-type: none"> 60% in the ETN 50-mg BIW group 56% in the ETN 25-mg BIW group 14% in the ETN 25-mg QW group 53% in the placebo/ETN 25-mg BIW group 	<p>Gordon, Kenneth B., et al. "Clinical response in psoriasis patients discontinued from and then reinitiated on etanercept therapy." <i>J Dermatolog Treat</i>, vol 17, 2006, pp. 9-17. Available from: https://pubmed.ncbi.nlm.nih.gov/16467018/</p>
<p>Description</p> <ul style="list-style-type: none"> Global phase 3 Dose reduction at week 12 24-week study N = 583 	<p>Study Arms</p> <ul style="list-style-type: none"> ETN 50 mg BIW/ETN 25 mg BIW ETN 25 mg BIW/ETN 25 mg BIW Placebo/ETN 25 mg BIW 	<p>Key Results</p> <ul style="list-style-type: none"> At week 12, proportion of patients achieving PASI 75 <ul style="list-style-type: none"> 49% in the ETN 50-mg group (p < 0.0001) 34% in the ETN 25-mg group (p < 0.0001) 3% in the placebo At week 24 (12 weeks after switch), proportion of patients achieving PASI 75 <ul style="list-style-type: none"> 54% in the ETN 50-mg/25-mg group 45% in the ETN 25-mg/25-mg group 28% in the placebo/ ETN 25-mg group 	<p>Publications</p> <p>Papp, Kim A., et al. "A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction." <i>BJD</i>, vol152, 2005, pp. 1304. Available from: https://academic.oup.com/bjd/article-abstract/152/6/1304/6636754?redirectedFrom=fulltext&login=false</p>

BIW = twice weekly; ETN = etanercept; PASI = Psoriasis Area and Severity Index; QW = once weekly; RCT, randomized controlled trial; US, United States. *not an FDA-approved dosage

Table 6. Current Cost of Existing Therapeutic Alternatives

Description	Maintenance Dose for RA	Annual List Price
HUMIRA INJECTION 2 PREFILLED PEN 0.4 ML 40 MG	40 MG x 1 dose every 2 Weeks for 365 Days	\$ 90,241
SIMPONI INJECTION 1 PREFILLED SYRINGE 1 ML 100 MG	100 MG x 1 dose every 1 Month for 365 Days	\$ 82,095
ENBREL INJECTION 1 PREFILLED PEN 1 ML 50 MG	50 MG x 1 dose every 1 Week for 365 Days	\$ 91,893
Cimzia	No data available	No data available
REMICADE INFUSION 1 LYOPHILIZED POWDER VIAL 10 ML 100 MG	5 MG/Kg x 1 dose every 42 Days for 323 Days	\$ 43,696
ORENCIA INJECTION 4 PREFILLED PEN 1 ML 125 MG	125 MG x 1 dose every 1 Week for 365 Days	\$ 70,040
XELJANZ TABLETS 1 PACK 60 TABS 10 MG	10 MG x 2 dose every 1 Day for 365 Days	\$ 67,084
RINVOQ EXTENDED RELEASE TABLETS 1 PACK 30 TABS 30 MG	30 MG x 1 dose every 1 Day for 365 Days	\$ 74,520
ACTEMRA INJECTION 1 PREFILLED PEN 0.9 ML 162 MG	162 MG x 1 dose every 1 Week for 365 Days	\$ 59,474
Kevzara	No data available	No data available

Source: From 20230718 - SSR Health Data[93].xlsx (full details); and SSR Inflamm GTN Pull 7.18[96].xlsx (summarized) - Supplied by Amgen

Table 7: Additional Literature Reporting Safety Outcomes Dec 2014-March 2019

Title	Summary	Reference
Multiple Indications		
Risk of drug-induced liver injury from tumor necrosis factor antagonists.	Of TNF blockers, INF is associated most frequently with drug-induced liver injury, developing in 1 of 120 patients who received INF; 1 in 430 patients who received ETN.	Björnsson, Einar S et al. "Risk of drug-induced liver injury from tumor necrosis factor antagonists." <i>Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association</i> vol. 13,3 (2015): 602-8. doi:10.1016/j.cgh.2014.07.062
Risk of malignancies using anti-TNF agents in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: a systematic review and meta-analysis.	The subgroup analysis, according to the type of TNF blocker, did not demonstrate any statistically significant association between ETN and cancer risk.	Bonovas, Stefanos et al. "Risk of malignancies using anti-TNF agents in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: a systematic review and meta-analysis." <i>Expert opinion on drug safety</i> vol. 15,sup1 (2016): 35-54. doi:10.1080/14740338.2016.1238458
Low risk of birth defects for infants whose mothers are treated with anti-tumor necrosis factor agents during pregnancy.	In a register-based study, infants born to women treated with ETN for chronic inflammatory disease (N=344) had a slightly, but not significantly, increased risk of birth defects compared with infants born to women with similar disease but no TNF blocker treatment (odds ratio: 1.49 [95% CI, 0.92–2.28]).	Bröms, Gabriella et al. "Low Risk of Birth Defects for Infants Whose Mothers Are Treated With Anti-Tumor Necrosis Factor Agents During Pregnancy." <i>Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association</i> vol. 14,2 (2016): 234-41.e1-5. doi:10.1016/j.cgh.2015.08.039
Real-world comparative risks of herpes virus infections in tofacitinib and biologic-treated patients with rheumatoid arthritis.	The rate of zoster associated with tofacitinib was approximately double that observed in patients using biologics, including ETN, which had the lowest reported incidence rate.	Curtis, Jeffrey R et al. "Real-world comparative risks of herpes virus infections in tofacitinib and biologic-treated patients with rheumatoid arthritis." <i>Annals of the rheumatic diseases</i> vol. 75,10 (2016): 1843-7. doi:10.1136/annrheumdis-2016-209131
Pregnancy outcome following gestational exposure to TNF-alpha-inhibitors: A prospective, comparative, observational study.	An observational study including 25 pregnant women exposed to ETN showed that TNF blocker treatment does not pose a major teratogenic risk.	Diav-Citrin, Orna et al. "Pregnancy outcome following gestational exposure to TNF-alpha-inhibitors: a prospective, comparative, observational study." <i>Reproductive toxicology (Elmsford, N.Y.)</i> vol. 43 (2014): 78-84. doi:10.1016/j.reprotox.2013.11.004
Risk of solid cancer in patients exposed to	A cohort study comparing the risk of solid cancer in patients with RA treated with	Mercer, Louise K et al. "Risk of solid cancer in patients exposed to anti-

Title	Summary	Reference
<p>antitumour necrosis factor therapy: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis.</p>	<p>TNF blockers (N = 11,767) to that in patients treated with cDMARDs (N = 3249) showed that addition of ETN to cDMARD does not alter the risk of cancer in RA patients selected for TNF blockers.</p>	<p>tumour necrosis factor therapy: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis." <i>Annals of the rheumatic diseases</i> vol. 74,6 (2015): 1087-93. doi:10.1136/annrheumdis-2013-204851</p>
RA		
<p>The effect of etanercept on traditional metabolic risk factors for cardiovascular disease in patients with rheumatoid arthritis.</p>	<p>An evaluation of CVD risk factors as an exploratory endpoint in a phase 4, prospective, randomized, double-blind, placebo-controlled study revealed that treatment with ETN did not adversely affect levels of metabolic risk factors for CVD in patients with RA.</p>	<p>Deodhar, Atul et al. "The effect of etanercept on traditional metabolic risk factors for cardiovascular disease in patients with rheumatoid arthritis." <i>Clinical rheumatology</i> vol. 35,12 (2016): 3045-3052. doi:10.1007/s10067-016-3422-7</p>
<p>Re-initiation of biologics after the development of tuberculosis under anti-TNF therapy.</p>	<p>A retrospective chart review of patients using TNF blockers (N = 2754) who developed TB (N = 22) examined outcomes after re-initiation of biologic agents following withdrawal of TNF blockers because of active TB; 87% of TB cases occurred during treatment with monoclonal agents, especially INF. Three patients were receiving ETN at the time of TB diagnosis. After TB diagnosis, ETN was started in 6 patients (duration of re-treatment: 20 to 83 months). One of these, who had received INF initially, received ETN for 15 months and was switched to canakinumab because of inadequate response. After the third dose of canakinumab, this patient had TB relapse. Data suggest that TNF blockers can be restarted when clinically indicated.</p>	<p>Ozguler, Yesim et al. "Re-initiation of biologics after the development of tuberculosis under anti-TNF therapy." <i>Rheumatology international</i> vol. 36,12 (2016): 1719-1725. doi:10.1007/s00296-016-3575-3</p>
<p>Evaluation of the immunogenicity of the 13-valent conjugated pneumococcal vaccine in rheumatoid arthritis patients treated with etanercept.</p>	<p>In RA patients treated with ETN, vaccination with PCV13 is effective and safe.</p>	<p>Rákóczi, Éva et al. "Evaluation of the immunogenicity of the 13-valent conjugated pneumococcal vaccine in rheumatoid arthritis patients treated with etanercept." <i>Joint bone spine</i> vol. 83,6 (2016): 675-679. doi:10.1016/j.jbspin.2015.10.017</p>
<p>Risk of gastrointestinal perforation among rheumatoid arthritis patients receiving</p>	<p>In a cohort study evaluating GI perforation in RA patients receiving tofacitinib, TCZ, or other biologic agent, the incidence rate (95% CI) of hospitalized GI perforation per</p>	<p>Xie, Fenglong et al. "Brief Report: Risk of Gastrointestinal Perforation Among Rheumatoid Arthritis Patients Receiving Tofacitinib, Tocilizumab, or</p>

Title	Summary	Reference
tofacitinib, tocilizumab, or other biologics.	1000 patient-years in RA patients treated with ETN was 0.74 (0.51–1.07) for all GI perforation, 0.47 (0.30–0.75) for lower GI tract perforation, and 0.26 (0.14–0.49) for upper GI tract perforation. The study showed a > 2-fold increased risk of lower GI tract perforation among TCZ users compared to patients receiving TNF blockers.	Other Biologic Treatments.” <i>Arthritis & rheumatology (Hoboken, N.J.)</i> vol. 68,11 (2016): 2612-2617. doi:10.1002/art.39761
Risks of herpes zoster in patients with rheumatoid arthritis according to biologic disease modifying therapy.	A retrospective cohort study among RA patients showed that among older patients with RA, the risk of HZ was similar across biologic agents, including those with different mechanisms of action. HZ was reported in 48 of 2229 patient-years treated with ETN (absolute incidence rate = 2.15/100 patient-years [95% CI: 1.62, 2.86], adjusted HR relative to abatacept = 1.26 [95% CI: 0.87, 1.81]).	Yun, Huifeng et al. “Risks of herpes zoster in patients with rheumatoid arthritis according to biologic disease-modifying therapy.” <i>Arthritis care & research</i> vol. 67,5 (2015): 731-6. doi:10.1002/acr.22470
The risk of gastrointestinal perforations in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the BSRBR-RA.	In a cohort study of the incidence of GI perforations (GIP) in RA subjects treated with TNF blocker therapy (N = 11,881) or cDMARDs (N = 3393), there was no statistically significant association between TNF blocker treatment, including ETN (N = 4129), and the risk of GIP (adjusted HR for ETN relative to cDMARD) = 1.8 [95% CI: 0.5 to 7.5]).	Závada, Jakub et al. “The risk of gastrointestinal perforations in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the BSRBR-RA.” <i>Annals of the rheumatic diseases</i> vol. 73,1 (2014): 252-5. doi:10.1136/annrheumdis-2012-203102
PsO		
OBSERVE-5: observational post marketing safety surveillance registry of etanercept for the treatment of psoriasis final 5-year results.	A 5-year observational post marketing safety surveillance registry of ETN for the treatment of PsO assessing key outcome measures has been completed. This study showed a 5-year cumulative incidence (95% CI) of 5.2% (4.1%, 6.2%) for serious infectious events requiring hospitalization, which was not higher than expected relative to administrative claims data. In another study, the incidence of hospitalized infectious events from 2005 to 2009 was evaluated in patients with PsO treated with ETN (N = 6166) based on data from a commercial claims database ²⁸⁷ . The incidence rate (95% CI) of	Kimball, Alexa B et al. “OBSERVE-5: observational post marketing safety surveillance registry of etanercept for the treatment of psoriasis final 5-year results.” <i>Journal of the American Academy of Dermatology</i> vol. 72,1 (2015): 115-22. doi:10.1016/j.jaad.2014.08.050 Kimball AB, Schenfeld J, Accortt NA, et al. Incidence rates of malignancies and hospitalized infectious events in patients with psoriasis with or without treatment and a general population in the U.S.A.: 2005-09. <i>Br J Dermatol.</i> 2014;170:366-373

Title	Summary	Reference
	<p>hospitalized infectious events per 10,000 person-years over a median average follow-up of 0.54 years was 191 (142, 240).</p>	
<p>Psoriatic arthritis treatment and the risk of herpes zoster.</p>	<p>A retrospective cohort study evaluated the association between cDMARDs or TNF blockers and HZ in 3128 patients with PsA. The study showed that compared with the rate of HZ events/1000 treatment-years in patients not treated with cDMARDs (7.36 [95% CI: 5.41, 9.79]), the rate was greater in patients treated with the combination of ETN + cDMARDs (27.80 [95% CI: 12.71, 52.78]) but not in patients treated with ETN administered separately (9.18 [95% CI: 3.96, 18.08]).</p>	<p>Zisman, D et al. "Psoriatic arthritis treatment and the risk of herpes zoster." <i>Annals of the rheumatic diseases</i> vol. 75,1 (2016): 131-5. doi:10.1136/annrheumdis-2013-205148</p>
PsA		
<p>Cardiovascular effects of etanercept in patients with psoriatic arthritis: evidence from the cardiovascular risk in rheumatic diseases database.</p>	<p>The cardiovascular effects of ETN in patients with PsA were evaluated in a post hoc subanalysis of the Cardiovascular Risk in Rheumatic Diseases (CaRRDs) database. The study demonstrated that patients receiving ETN, who achieved minimal disease activity showed a platelet reactivity comparable to healthy controls. Similarly, the anti-inflammatory effect of ETN was associated with a significant improvement of hemostatic and fibrinolytic parameters, maximal changes being documented in patients achieving minimal disease activity. In addition, treatment with ETN seemed to be associated with a carotid intima-media thickness significantly lower than that in matched patients receiving cDMARDs. These data suggest a potential cardioprotective effect of ETN.</p>	<p>Di Minno, Matteo Nicola Dario et al. "Cardiovascular effects of Etanercept in patients with psoriatic arthritis: evidence from the cardiovascular risk in rheumatic diseases database." <i>Expert opinion on drug safety</i> vol. 14,12 (2015): 1905-13. doi:10.1517/14740338.2015.1111870</p>

TNF = tumor necrosis factor; INF = infliximab; cDMARD = conventional disease-modifying antirheumatic drug; HZ = herpes zoster; CVD = cardiovascular disease; TB = tuberculosis; ETN = etanercept; INF = infliximab; RA = rheumatoid arthritis; PsO = psoriasis; PsA = psoriatic arthritis; TCZ = tocilizumab; PCV13 = pneumococcal conjugate vaccine 13

Enbrel Citations

Question 28

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Question 29

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Public E2 Submission

IPAY: 2026

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

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Question	Sub-Question	Response
Question 29: 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? What type of Evidence is shown?	
Question 30: Addressing Unmet Medical Needs	Response to Question 30	
	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? What type of Evidence is shown?	

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Question	Sub-Question	Response
Question 31: Patient and Caregiver Experience	Response to Question 31	<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 can negatively affect older adults' health and financial security. [REDACTED] a Medicare enrollee from [REDACTED], is living with a health condition and takes Enbrel to treat the condition. When he could not afford the annual \$5,000 to \$6,000 out-of-pocket cost, [REDACTED] skipped his medication. "I would not pay it. I would just have to try to find a way around it. Do you want to eat?" [REDACTED] has said that the constant chronic pain impacted his physical, mental, and spiritual health. "It's very difficult to be a spiritual person when you are in horrible pain all the time." ..AARP fiercely believes that the needs of Medicare beneficiaries should remain paramount as the agency implements the Negotiation Program. In 2022, about 1 in 5 adults ages 65 and up either skipped, delayed, took less medication than was prescribed, or took someone else's medication last year because of concerns about cost. It is not fair or right to ask patients and taxpayers to continue paying for high prescription drug prices that are the result of broken markets. ..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</p>

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Question	Sub-Question
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Question	Sub-Question	Response
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Question	Sub-Question	Response
		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 ...Sincerely, ..Nancy LeaMond.Executive Vice President and Chief Advocacy & Engagement Officer

		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 ...Sincerely, ..Nancy LeaMond.Executive Vice President and Chief Advocacy & Engagement Officer
Question 32: Executive 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.¹ 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).² 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 2006.³ Further, the median price of a new brand-name prescription drug is now approximately \$200,000 per year,⁴ 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 can negatively affect older adults' health and financial security. █████, a Medicare enrollee from █████, is living with a health condition and takes Enbrel to treat the condition. When he could not afford the annual \$5,000 to \$6,000 out-of-pocket cost, █████ skipped his medication. "I would not pay it. I would just have to try to find a way around it. Do you want to eat?" █████ has said that the constant chronic pain impacted his physical,

¹ 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>.

² *Id.*

³ *Id.*

⁴ 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/>.

mental, and spiritual health. “It’s very difficult to be a spiritual person when you are in horrible pain all the time.”

AARP fiercely believes that the needs of Medicare beneficiaries should remain paramount as the agency implements the Negotiation Program. In 2022, about 1 in 5 adults ages 65 and up either skipped, delayed, took less medication than was prescribed, or took someone else’s medication last year because of concerns about cost.⁵ It is not fair or right to ask patients and taxpayers to continue paying for high prescription drug prices that are the result of broken markets.

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,⁶ reduce the budget deficit by \$25 billion in 2031,⁷ and save Medicare Part D enrollees \$7 billion in 2031 due to lower out-of-pocket costs and premiums.⁸

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.

Sincerely,



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

⁵ Stacie B. Dusetzina et al., “Cost-Related Medication Nonadherence and Desire for Medication Cost Information Among Adults Aged 65 Years and Older in the US in 2022,” *JAMA Network Open* 6, no. 5 (2023): e2314211, <https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2805012>.

⁶ 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. Accessed September 27, 2023.

⁷ 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.

⁸ *Id.*

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Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	ETANERCEPT
	Q26 - Respondent Name	
	Q26 - Organization Name (if applicable)	AiArthritis (International Foundation for Autoimmune & Autoinflammatory Arthritis)
	Respondent Email Who is completing this form?	PAO
Question 27: Prescribing Information	Prescribing Information	<p>Etanercept is approved for the following AiArthritis disease indications: Rheumatoid Arthritis, Psoriatic Arthritis, Axial Spondyloarthritis (Ankylosing Spondylitis), Juvenile Idiopathic Arthritis, and is used off-label for the following AiArthritis diseases: Behcet's Disease and Sarcoidosis. Etanercept was the first anti-tumor necrosis factor (anti-TNF) agent approved by the FDA to treat rheumatoid arthritis. [1] These are one type of Mechanism of Action (MoA) that targets our diseases. Many rheumatologists prefer prescribing treatments with long-term established effectiveness (particularly TNF inhibitors). [2]..Regarding how this drug is used for the disease treated by each indication, we would like to take this opportunity to point out that within each AiArthritis disease diagnosis, there is a spectrum of disease that is dependent on many confounding factors, such as:..-Age of the person when onset originates. While the average age of onset for AiArthritis diseases is 20 to 40 in adults, and any age in children (even at birth), onset can happen at any age. ..-Year the person was diagnosed. This is hugely important to consider, as those diagnosed prior to the age of biologics (late 1990's), which is a large percentage of those currently on Medicare, would not have had access to early and effective therapy. As a result, they are highly likely to have extensive damage (joints, organs, tissues), experience comorbidities (dual, triple or more autoimmune diseases, heart disease, Alzheimer's disease, dementia), and a history of operations (such as joint replacements). Given they missed the "window of opportunity" (see below), they are highly likely to require use of biologics to manage their disease for the rest of their lives (high costs of the medications for life equals high cost to Medicare)..However, over recent years a new subgroup of AiArthritis diseases have emerged, called Last Onset (Psoriatic Arthritis, Rheumatoid Arthritis). See Section 1, Q29 for more details. ..-The window of opportunity: Duration of onset to diagnosis, initial treatment, treatment that works for the patient. The American College of Rheumatology (ACR) recommends early intervention with disease modifying agents as early as 6 months after onset for the best opportunity to achieve remission in people diagnosed with AiArthritis diseases. However, diagnosing these diseases rarely occurs within this time frame for a variety of factors including, but not limited to: 1) delay in detection 2) delay in referral to a specialist 3) access to specialists (health equity, lack of specialists, rural areas). ..-The average time to diagnose these diseases varies, but ranges between 1 and 9 years. Fixing the issue of early diagnosis and</p>

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therapy will increase rates of remission and enable many patients to discontinue use of expensive therapies, like biologics...-Mild, Moderate, Severe. There are also varying degrees of disease severity. Biologics are used largely to treat moderate to severe disease, which is most common. Those with severe disease are most prone to worse outcomes and comorbidities, especially if their treatment is disrupted or they are not matched with the best therapy for their unique needs early on..-Comorbidities. An estimated 50% or more of people with one AiArthritis disease will develop at least one more autoimmune/autoinflammatory disease, which happens when inflammation is uncontrolled. [3] Uncontrolled inflammation is also responsible for potentially developing heart disease, interstitial lung disease, Alzheimer's disease, and dementia. [4] [5]..-Disease complexity. AiArthritis cannot express enough that a diagnosis does not dictate how a disease manifests in any one condition. For example, Juvenile Idiopathic Arthritis often involves inflammation of the eyes (uveitis), but may not be present in all. Choosing a biologic, in this case, may be dependent on which demonstrates higher efficacy and safety in people with uveitis...The American College of Rheumatology (ACR), the governing scientific authority on determining disease therapeutic recommendations, revised their recommendations for treating Rheumatoid Arthritis in 2021. .Both Due to the heterogeneous nature of RA and similar conditions, the following recommendation was added: "Patients who haven't been previously treated with a biologic or small molecule drug should be managed using a "treat-to-target" (T2T) approach." [6] T2T is a strategy that defines a treatment target (such as remission or low disease activity) and applies tight control (for example, monthly visits and respective treatment adjustment) to reach this target. The treatment strategy often follows a protocol for treatment adaptations depending on the disease activity level, comorbidities, and degree of response to treatment. ..This is important to note, as research over the past decade has demonstrated when a rheumatology patient works with their rheumatologist using the T2T approach, the chances to obtain disease control and the opportunity to achieve remission increase significantly.[7] [8] Therefore, although this recommendation was put forth in regards to RA, it can be applied to any of the diseases mentioned above, as outlined in Treat-to-Target as an approach in inflammatory arthritis. [9] ..Prior to the utilization of a T2T approach, the word remission was relatively unheard of for the large majority of patients living with moderate to severe AiArthritis diseases. Over the past few years, research has demonstrated when patients are treated early and have high efficacy responses to treatments - which may require working with their rheumatologist to alter therapies and types of biologic targets (i.e., stay on a TNFi, like Enbrel). *MoA switching to get disease under control, but not ok to switch to different drugs with the same MoA (different inactive ingredients, different method of application, etc.) ..Process of finding the right treatment (Trial and Error). In addition to all the factors previously mentioned, CMS must also consider the process it takes to find a treatment that works.* Biologics take, on average, 3 months to determine if they are working or if a patient should work with their doctor to reassess and prescribe a new therapy. (See T2T approach, Section 1, Q27). At this point, several factors can dictate if therapy can be switched, largely including access to specialists/frequency of visits and accessibility of the doctor recommended treatment on the insurance plan formulary. As a result, the average patient will try and fail 2 to 3 biologics before finding the one that works best for them. This process factors

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Question	Sub-Question	Response
	<p>Evidence Submitted include a cost-effectiveness measure?</p> <p>What type of Evidence is shown?</p>	<p>into why continuity of care is vital (once the right medication is found) and in consideration why comorbidity progression may happen...*This includes working well enough to achieve remission or, at the least if remission isn't possible, the best possible quality of life...What matters to patients. AiArthritis is the only patient organization in the world that focuses on the group of autoimmune and autoinflammatory disease inclusive of inflammatory arthritis as a major clinical component and whose leaders are all either living with the conditions or, in one case, is a caregiver for a person struggling to get diagnosed ("the undiagnosed", a large portion of our population who represent delays in detection, referrals, diagnosis). From a patient perspective, if a drug is working well for us (we are stable), there should be no alternatives. Disrupting continuity of care when continued stability cannot be guaranteed is ethically questionable...CITATIONS:.1. Gerriets, Valerie, et al. "Tumor Necrosis Factor Inhibitors." StatPearls, StatPearls Publishing, 1 Jan. 2023. Updated 3 Jul. 2023, www.ncbi.nlm.nih.gov/books/NBK482425/. Accessed 1 Oct. 2023..2. Barnard, Claire. "'The Great Debate': JAK inhibitors vs biologics following methotrexate failure in RA." Medicine Matters Rheumatology, 11 Nov. 2020, rheumatology.medicinematters.com/acr-2020/rheumatoid-arthritis-/the-great-debate-jak-inhibitors-biologics-ra/18576196.</p> <p>N</p>
<p>Question 28: Therapeutic Impact and Comparative Effectiveness</p>	<p>Therapeutic Impact and Comparative Effectiveness</p>	<p>AiArthritis understands the purpose of this initial phase of data collection is, in part, to determine if there are alternatives to treatments currently covered by Medicare Part D that could be substituted to save costs to patients and the Medicare system. We also realize the goal is to establish a Maximum Fair Price (MFP), not to pull access from a medication already working well for the patient. However, we are concerned patients on Enbrel- and who are stable on them - will lose access if CMS does not realize the importance of continuity of care in those living with AiArthritis diseases. For this reason, we would like to take this opportunity to explain why continuity of care is vital in this population...AiArthritis feels obligated to also mention that any price negotiations that result in a patient's loss of access to Enbrel, and if stable on this treatment, could have dire results for both the patient and the healthcare system. Delayed access to treatments, including disrupting continuity of care by switching a stable patient to another treatment, can disrupt the immune response and cause unnecessary disease instability and progression (harm). ..AiArthritis diseases, which are heterogeneous (unique to individuals and subgroups). They are caused by issues within the body's immune system, which is complex and requires regulation when overactivity causes uncontrolled inflammation. [1] Therefore, people diagnosed with the same disease (i.e. psoriatic arthritis, Axial Spondyloarthritis (Ankylosing Spondylitis), Juvenile Idiopathic Arthritis), will not all respond the same way to a drug approved by the FDA to treat it. This issue is exacerbated by clinical trial design, which historically excludes people with comorbidities (which are common in our diseases) and lack demographic representation.[2] As a result, once a drug gets to market,</p>

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while it may work for many patients, it equally will not work for others. So the process to find the right medication is complicated, often requiring a lengthy trial-and-error process. (See Section 1, Q27: Trial and error process)...For example, a person who was diagnosed over 20 years ago, who has significant damage to their joints and has developed multiple comorbidities - such as another AiArthritis disease, heart disease, or other organ complication - experiences a different "rheumatoid arthritis" journey than a person diagnosed a year ago and treated early with an effective therapy. (See Section 1, Q27: AiArthritis disease diagnosis, there is a spectrum of disease that is dependent on many confounding factors)...In another study, patients with RA with higher continuity of rheumatology care had lower rates of Emergency Department (ED) visits and hospitalizations compared to those who did not receive continuous rheumatology care during the first 5 years of follow-up. These findings provide evidence to support the value of early and continuous rheumatology care for reducing hospitalizations and ED visits.[3]..In Enbrel's Condition Management Guide,[4] a medical study was cited which stated after 5 years over half of patients taking Enbrel had no additional joint damage. At AiArthritis, we are led by people living with diseases and who use biologics to manage our conditions. For this reason, we feel it is important to note people were on the biologic for 5 or more years. Many times a biologic either stops working after 2 or 3 years, or through the process of T2T, a patient and doctor decide to try another therapy option. If a person is on a biologic for this long, they must be experiencing continuity of care. We heard similar stories of longevity with Enbrel during the Colorado Prescription Drug Affordability Board reviews (September 2023), one citing 5 years and another 6 years. ..We would also like to highlight a statement in the same guide, following the data mentioned above. "People who do not respond at 3 months are unlikely to respond to Enbrel." This information is in keeping with treatment protocols recommended for AiArthritis disease patients, which include a T2T approach until continuity of care is achieved. ..There are many examples of published articles to show patient-reported outcomes and sustained efficacy and safety in etanercept after 5 years, including in patients with Axial Spondyloarthritis/Ankylosing Spondylitis [5]. But we would like to take the opportunity to provide you with a sample of patient testimony regarding its efficacy and what that means to them:.."Before I was on this drug, I was struggling to maintain any real quality of life. I honestly don't know how I raised a family and pushed through the pain and fatigue for so many years. I guess I thought this was just my new normal and I'd have to live with it. When I switched rheumatologists, she suggested we switch medications and Enbrel was the one my insurance company said to try. Given I was failing the other one, I was happy to give it a whirl! WOW - in just about a month I felt better than I had in years! For some people, it may seem like small things, like I could go on walks with my husband after dinner and not have to worry about how I would get home if I walked too far. Or being able to hold my granddaughter in my arms for more than a few minutes. I've been on this drug now for over 3 years and if my Medicare plan decided to take it away from me now, I'd be devastated. I don't understand how any company without data on ME can justify forcing me to leave behind a miracle and gamble on my life."..."While I am no longer taking this drug, it was my magic bullet for years. I think due to menopause my hormones changed and it affected my immune response to the drug. I was on it for 15 years and then it stopped working. It took over 2 years to find something else that worked for

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Question	Sub-Question	Response
	<p data-bbox="262 646 609 889">Hyperlink to Table/Charts/Graphs - Additional Materials for Question 28 Evidence Submitted include a cost-effectiveness measure?</p> <p data-bbox="262 933 609 998">What type of Evidence is shown?</p>	<p data-bbox="609 251 1971 641">me, but that trial and error process was a nightmare. I know the same biologic can work wonders for one person and do nothing for the next, so I'm grateful it worked for me as long as it did. I believe that is why I have not had joint replacements like many of my friends."..Statement on biosimilars. While researchers have expressed there are not significant changes in immune responses when switching from the reference product to a biosimilar, most rheumatologists in the United States (and patients, too) are still concerned any time a stable patient is switched drugs without consultation with their doctor (as many factors, as outlined elsewhere in these statements must be considered outside of one disease diagnosis). Additionally, switching can sometimes lead to an increase in total healthcare costs, which is a crucial consideration. [6] [7] ..We are also unclear how these IRA negotiations and FMP evaluations will consider biosimilars as they come to market. We are excited about biosimilars, which we hope will improve access and lower costs, but we are concerned how the pricing caps will impact their rollout.</p> <p data-bbox="609 860 661 893">N</p>
<p data-bbox="63 1201 262 1372">Question 29: Comparative Effectiveness on Specific Populations</p>	<p data-bbox="262 1274 609 1307">Response to Question 29</p>	<p data-bbox="609 1039 1971 1533">Persons with disabilities. "Persons with disabilities often experience a wide and varying range of health conditions that lead to poorer health and shorter lifespan. In addition, discrimination, inequality, and exclusionary structural practices, programs, and policies create barriers to timely and comprehensive health care, which further results in poorer health outcomes. People with disabilities who also belong to one or more other populations with health disparities fare even worse." This is a quote taken from the September 2023 announcement by the National Institute on Minority Health and Health Disparities that people with disabilities will be designated as their own health disparity population.[1] This is, in part, due to recognition work needs to be done to better understand the complexities that lead to worse outcomes and the need for multilevel interventions. ..Elderly-onset Rheumatoid Arthritis (EORA), Psoriatic Arthritis (EOPsA). While typically people with AiArthritis diseases, like RA, experience adult onset between the ages of 20 and 40, there is a new subgroup of RA (EORA) that affects persons over the age of 60.[2] It is often characterized by acute onset and high disease activity (positive for antibodies that signal worse disease and outcomes and presence of bone erosions). As people age, bone density diminishes and the immune system weakens. Comorbidities that are common in uncontrolled AiArthritis diseases (such as heart disease, interstitial lung disease, Alzheimer's, and</p>

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dementia), can also occur as one ages. This puts this subpopulation in particular risk for worse outcomes. Treatment for EORA AiArthritis would also like to point out that this phenomenon is not only occurring in RA, but also in other AiArthritis diseases, like Psoriatic Arthritis and Spondyloarthritis [3][4]..Investigating Associations Between Access to Rheumatology Care, Treatment, Continuous Care, and Healthcare Utilization and Costs Among Older Individuals. Research was conducted to examine the association between rheumatologist access, early treatment, and ongoing care of older-onset rheumatoid arthritis (RA) and healthcare utilization and costs following diagnosis. Access to rheumatologists for RA diagnosis, timely treatment, and ongoing care (continuity of care) are associated with lower total healthcare costs at 5 years. Investments in improving access to care may be associated with long-term health system savings. While this study was conducted in persons with EORA, the findings are relevant for other diseases, like Psoriatic Arthritis, where time to diagnosis and treat, as well as treatments used, are similar.[5] ..Treat-to-Target (T2T) versus Usual Care. Current consensus amongst the rheumatology community is that a T2T strategy should be used when treating people with AiArthritis diseases. (See T2T approach, Section 1, Q27). An example of usual care would consist of visiting a rheumatologist or other specialist who is not closely monitoring disease activity and who is not altering therapies regularly to achieve better outcomes...Complexities of diseases, including subgroups and disease-specific domains. As mentioned throughout our comments, our diseases themselves are complex and consist of many domains to consider when choosing a treatment. (See Section 1, Q27: Complexity of disease domains, see attached chart)...AiArthritis, an organization led by patients, would like CMS to consider the cost savings associated with a T2T approach. From personal experience, we understand the value associated with patient-rheumatologist/specialist targeted treatments (which includes more doctor visits initially, but less poorer outcomes and additional specialists treatments/comorbidity development long term). ..While the switch recommended was still in the same biologic MoA (IL-17i), any switch from a stable disease state is strongly not recommended - for any reason. Even if a biologic (or biosimilar) targets the same thing there are other factors to consider, such as 1) method of application (injection needed versus pen, infusion versus injection) or 2) inactive ingredients/methods of manufacturing, which can cause an immune response. Additionally to consider, once a stable AiArthritis disease patient is pulled from a biologic treatment, it's possible if they try to go back to the original medication it will no longer be as effective. While many studies, for example with biosimilars, show switching from the reference product to a biosimilar is safe, because of patient experience and testimony within our own organization - which speaks annually with thousands of patients worldwide - we do not endorse switching a stable patient to either a different biologic (same MoA, or otherwise) or a biosimilar...Precision medicine. Precision medicine, which is the integration of clinical research and a patient's biologic makeup (biomarkers - blood, tissues), is moving quickly into the rheumatology space. As more research is done into patient subgroups, data will enable doctors (and payers) to better understand which treatments will, or will not, work best for a patient - potentially eliminating the current trial and error process and improving the chance for drug-free remission. (See trial and error process, Section 1, Q27)..AiArthritis would also like CMS to consider the following in regards to cost:.Enbrel - One

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reason Enbrel is one of the most costly is because most people start with Enbrel in their diagnosis journey. This is largely in part to what Medicare and other insurance companies place on their formularies. Whether it is the first treatment after diagnosis, or required as part of a step therapy fail first protocol, most people will be prescribed Enbrel before accessing any other drug. As outlined previously, Enbrel - nor any other biologic or biosimilar - should be forced on a patient without their doctor, who is ethically obligated to treat to the unique characteristics of the patient [6] . If Enbrel is the priority drug on the formulary and either 1) it is the patient's first time trying a biologic or 2) the patient is not doing well on their current biologic AND they historically have done well on anti-TNF MoA's or 3) the patient is not doing well on their current biologic AND there is no known history if they will do well, or not, or an anti-TNF drug, then it is acceptable to follow step therapy protocols. However, if 1) the patient is stable on an existing therapy or 2) the patient has tried and failed Enbrel prior or 3) the patient is known not to respond well to anti-TNF drugs, then Enbrel should not be used as a therapy forced by Medicare or other insurance plans. ..When Enbrel, or any other biologic treatment, does not follow the protocol for true safety and efficacy (as outlined above), it's the onus of CMS and the insurance company to fix the system that inevitably leads to Enbrel being on the 20% highest cost list. AiArthritis understands Pharmacy Benefit Managers (PBMs) are at the root of the negotiation process that establish formularies and that transparency is required first if the system has a chance of being fixed. So we encourage CMS to support any efforts around PBM transparency and reform as the first step to solving the high cost of these drugs...The second step CMS and payers can take to lower drug prices is to understand some diseases, like AiArthritis diseases, are not conducive to one-size-fits-all treatment plan. AiArthritis understands regulations must be in place to ensure physicians and patients do not continuously and regularly select higher cost options, but we also encourage those designing and implementing these protocols to remember doctors are also ethically responsible to consider cost in their recommendations. Unfortunately, doctors are not able to exercise that ethical duty in the case of AiArthritis diseases and biologic/biosimilar therapies...What matters to patients. "Our diseases are not one-size-fits-all, so just because one person is diagnosed with a condition does not mean the rest of the world diagnosed with that same condition is going to respond the same to a treatment. This is a vital flaw in formularies and the way treatments are matched to patients. Given our drugs make up 2 of 10 in the CMS high costs lists, one would think finding ways to eliminate trial and error and keep a patient stable would be the priority.".."Regarding accessibility and cost, there are many patients on Medicare Part D that used to be on biologics and had to stop using them when they started Medicare, simply because they can no longer use the manufacturer's copay assistance program while on a government program. I think CMS needs to consider what losing access to these treatments means for their community and will be willing to work with manufacturers to find solutions that are more affordable."

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Question	Sub-Question	Response
	Hyperlink to Citation - Additional Materials for Question 29	<p>Sugihara, Takahiko. "Treatment Strategies for Elderly-Onset Rheumatoid Arthritis in the New Era." <i>Modern Rheumatology</i>, vol. 32, no. 3, 2022, pp. 493-499, doi:10.1093/mr/roab087. https://academic.oup.com/mr/article-abstract/32/3/493/6430616?redirectedFrom=fulltext&login=false</p> <p>Caso, Francesco et al. "Late-Onset and Elderly Psoriatic Arthritis: Clinical Aspects and Management." <i>Drugs & aging</i> vol. 36,10 (2019): 909-925. doi:10.1007/s40266-019-00688-3</p> <p>Barber, Claire E H et al. "Investigating Associations Between Access to Rheumatology Care, Treatment, Continuous Care, and Healthcare Utilization and Costs Among Older Individuals With Rheumatoid Arthritis." <i>The Journal of rheumatology</i> vol. 50,5 (2023): 617-624. doi:10.3899/jrheum.220729</p> <p>Mougui, Ahmed et al. "Characteristics of Late-Onset Spondyloarthritis: Data from the Moroccan Registry of Biological Therapies in Rheumatic Diseases." <i>Cureus</i> vol. 15,5 e39100. 16 May. 2023, doi:10.7759/cureus.39100</p> <p>"Ethics of Step Therapy Investigation." <i>AiArthritis</i>, 2025, https://irp-cdn.multiscreensite.com/8f027529/files/uploaded/The%20Ethics%20of%20Step%20Therapy%202019.pdf. Accessed 2 Oct. 2023.</p> <p>"Health Disparities Population Designation." National Institute on Minority Health and Health Disparities, www.nimhd.nih.gov/about/directors-corner/messages/health-disparities-population-designation.html. Accessed 2 Oct. 2023</p>
	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: Addressing Unmet Medical Needs	Response to Question 30	n/a
	Hyperlink to Citation - Additional Materials for Question 30	<p>Immune System Overview." National Institute of Allergy and Infectious Diseases, www.niaid.nih.gov/research/immune-system-overview. Accessed 1 Oct 2023.</p> <p>Davtyan, Abel et al. "The Effects of Continuity of Rheumatology Care on Emergency Department Utilization and Hospitalizations for Individuals With Early Rheumatoid Arthritis: A Population-Based Study." <i>The Journal of rheumatology</i> vol. 50,6 (2023): 748</p>

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Question	Sub-Question	Response
	<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>	<p>Response</p> <p>Allocati, Eleonora et al. "Switching Among Biosimilars: A Review of Clinical Evidence." <i>Frontiers in pharmacology</i> vol. 13 917814. 24 Aug. 2022, doi:10.3389/fphar.2022.917814</p> <p>Martín-Mola, E et al. "Sustained efficacy and safety, including patient-reported outcomes, with etanercept treatment over 5 years in patients with ankylosing spondylitis." <i>Clinical and experimental rheumatology</i> vol. 28,2 (2010): 238-45.</p> <p>Addressing Demographic Disparities in Clinical Trials." <i>Harvard Business Review</i>, 2021, https://hbr.org/2021/06/addressing-demographic-disparities-in-clinical-trials. Accessed 2 Oct. 2023</p> <p>"Talk Show Ep88." <i>AiArthritis</i>, www.aiarthritis.org/talkshow-ep88. Accessed 2 Oct. 2023.</p> <p>"ENBREL Condition Management Guide." <i>Enbrel</i>, Accessed 2 Oct. 2023.</p>
Question 31: Patient and Caregiver Experience	Response to Question 31	
Question 32: Executive Summary	Response to Question 32	<p>AiArthritis diseases, like rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis, and juvenile arthritis are complex diseases that require close monitoring using a Treat-to-Target (T2T) approach to achieve low disease activity, potential remission, and the best opportunity to avoid comorbidities. Continuity of care is vital for patients, yet current insurance practices disregard this need and often, as a result, patients develop complications and may require lifelong treatment. AiArthritis strongly cautions CMS against switching any patient off of Enbrel/Stelara , or any other biologic if their disease is stable. ..While the drug under review contributes the top 20% of costs for Medicare Part D, we encourage CMS to consider other factors that lend to that position (i.e., step therapy/PBMs, placement on formularies/forced use). ..What matters to patients and their health is the most important factor to consider, so we hope CMS continues to expand their work to</p>

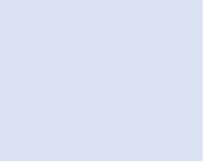
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Question

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Response

include patients in the negotiation process. We are concerned how the introduction of biosimilars and precision medicine will be considered as new medicines and research is introduced.

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Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	ETANERCEPT
	Q26 - Respondent Name	
	Q26 - Organization Name (if applicable)	Aimed Alliance
	Respondent Email	
Question 27: Prescribing Information	Who is completing this form?	PAO
	Prescribing Information	
	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	
	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	

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Question	Sub-Question	Response
Question 29: 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? What type of Evidence is shown?	
Question 30: Addressing Unmet Medical Needs	Response to Question 30	
	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? What type of Evidence is shown?	

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Question	Sub-Question	Response
Question 31: Patient and Caregiver Experience	Response to Question 31	
Question 32: Executive 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.¹ 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.² 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.³ 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.⁴ Aimed Alliance urges CMS to ensure patient and provider lived experiences are adequately valued when considering these factors and throughout this process.

¹ 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>

² *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>

³ *Id.*

⁴ <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.⁵ Sweden further incorporates ethical considerations, prioritizing those with the greatest health care needs and ensuring the process upholds and respects individual human dignity.⁶ By valuing the needs of patients and providers, Sweden maintains an overall high health care satisfaction rate.⁷ 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.⁸ 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.⁹

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.¹⁰ Aimed Alliance urges CMS to expand the number of listening

⁵ 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>.

⁶ Global Legal Rights, *Pricing & Reimbursement Laws and Regulations 2023*,

<https://www.globallegalinsights.com/practice-areas/pricing-and-reimbursement-laws-and-regulations/sweden>

⁷ 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>.

⁸ Houses of Parliament: Parliamentary Office of Science & Technology, *Drug Pricing*, https://www.parliament.uk/globalassets/documents/post/postpn_364_Drug_Pricing.pdf

⁹ *Id.*

¹⁰ 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.¹¹ While Aamed 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.¹² 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.¹³ For instance, one study found that out of 105 patients with IBD, 84 percent reported experiencing stigma associated with their condition.¹⁴ 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 if you have any additional questions.

Sincerely,
Ashira Vantrees
Counsel

¹¹ *Id.*

¹² 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/

¹³ 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/>

¹⁴ Marco Vinezco 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>

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Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	ETANERCEPT
	Q26 - Respondent Name	
	Q26 - Organization Name (if applicable)	Arthritis Foundation
	Respondent Email Who is completing this form?	PAO
Question 27: Prescribing Information	Prescribing Information	
	Evidence Submitted include a cost-effectiveness measure? What type of Evidence is shown?	
Question 28: Therapeutic Impact and Comparative Effectiveness	Therapeutic Impact and Comparative Effectiveness	<p>Methotrexate is considered first line therapy for most individuals with rheumatoid arthritis (RA). While many patients experience a reduction in symptoms while taking methotrexate, a sizable portion do not, or they are unable to achieve full remission. These individuals often add a biologic medication, and tumor necrosis factor inhibitors (TNFi) like Enbrel are now usually the first and most frequently used biologics for rheumatoid arthritis patients. ..While ACR's clinical guidelines for rheumatoid arthritis recommend the addition of a biological or targeted therapy over 'triple therapy' (addition of sulfasalazine and hydroxychloroquine) to patients who do not fully respond to methotrexate, there is not sufficient evidence to recommend a specific class of biologic or targeted therapy to start if a patient has not responded to methotrexate or other conventional disease modifying antirheumatic drug...While biomarker testing is available for rheumatoid arthritis patients, it is limited. PrismRA is currently the only CMS-covered biomarker test available that can help guide therapy decisions. Prism RA is a molecular signature response classifier blood test that can predict and individual RA patient's likelihood of inadequately responding to TNFi therapies, such as Enbrel. ..Our data shows wide heterogeneity and complexity in the autoimmune patient experience with biologics. The Arthritis Foundation participated in an Institute of Clinical and Economic Review (ICER) review of RA drugs in 2016-2017 and as part of this effort we conducted a survey of RA patients' experience with taking biologics. Among the findings: a majority had taken multiple biologics over the course of their RA and many switched early in treatment, including 56% of respondents who had been on or taken Enbrel for less than two years. The most</p>

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cited reason across all biologics was the drug didn't work. Specific to Enbrel, 48% cited it didn't work, 19% had bad side effects, and 9% had insurance changes. 35% of respondents indicated challenges accessing their medications and when asked the impact of insufficient treatment, 57% cited they had to take additional medications for things like pain, depression, and anxiety; 42% missed work or school; 40% experienced joint damage or worsening of disease; 22% developed non joint-related symptoms related to their disease; 19% had to leave their job or school; and 11% had to be hospitalized. ..As a result of this survey, ICER took into consideration the high level of variability in treatment efficacy and the consequences of disruptions of treatment and indicated in the final report that step therapy is not appropriate in all cases. ..We understand the negotiation process may alter market dynamics or shift incentives. This creates an important opportunity for CMS to ensure patient access to medicines and create appropriate guardrails, including limiting burdensome barriers such as prior authorization and step therapy. .Arthritis Foundation data demonstrates that inappropriate use of utilization management (UM) such as step therapy and prior authorization can lead to delays in care, resulting in negative financial, emotional, and physical consequences. Patients living with arthritis are particularly susceptible to these kinds of insurance practices, and many utilization management protocols tend to apply policies that do not adequately align with clinical guidelines or what the provider deems is in the patient's best interest. Inappropriate use of UM practices can lead to treatment delays and disease worsening. Step therapy, for example, occurs when health insurance practices require patients to try therapies preferred by the insurance company before approval for the therapy their doctor originally prescribed. When inappropriately used, step therapy can undermine the clinical judgment of health care providers and put patients' health at unnecessary risk. As indicated in our data above, many patients must try multiple drugs before finding one that works for them, so the ability to remain on a drug that works is critical..We encourage CMS to more explicitly define coverage requirements to reduce the risk of plans denying coverage for products critical to patients. It is crucial that CMS continuously works to ensure access and remove barriers to both negotiated and non-negotiated drugs that providers and patients agree are necessary and appropriate. We encourage CMS to clearly disseminate a definition of coverage requirements and future guidance and/or future proposed coverage-related rules. ..Enbrel is one drug in the class of biologics known as tumor necrosis alpha (TNF) inhibitor therapies. TNF inhibitors were the first biologics approved for rheumatoid arthritis and resulted a substantial improvement in patient outcomes compared to the conventional disease modifying antirheumatic drugs available at the time, such as methotrexate, hydroxychloroquine, among others. TNF inhibitors can also be combined with methotrexate to increase overall response rates. ..TNF inhibitors vary in their routes of administration. Enbrel is administered subcutaneously and patients can self-administer this medication in their home. Other TNF inhibitors such as infliximab/Remicade are administered by infusion and must be done so in a medical facility. ..Side effects from TNF inhibitors like Enbrel include an increased risk of severe infections and it is recommended that patients be screened for tuberculosis and viral hepatitis B and C before initiating these agents. Other side effects included increased risk of malignancies like lymphomas, congestive heart failure, demyelinating disorders, drug-induced lupus, and skin reactions.

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Question	Sub-Question	Response
	<p>Hyperlink to Table/Charts/Graphs - Additional Materials for Question 28 Evidence Submitted include a cost-effectiveness measure?</p>	<p>..Although individual TNF inhibitors are thought to have similar rates of infection, results from the Rheumatoid Arthritis-Observation of Biologic Therapy (RABBIT) prospective cohort study of 1529 patients with RA suggest that Enbrel/etanercept may be associated with lower rates of serious bacterial infection...There are varying reasons why a patient may prefer or need to take a biologic with one route of administration over another. A patient with severe hand deformities may have difficulty with self-administering their drug, for example, and therefore need to take a physician-administered medicine. Or a patient may not live near an infusion center and therefore need to take a biologic that is self-administered. We urge CMS to take these kinds of patient needs and considerations into account as you continue your process. ..The Arthritis Foundation will answer this question from the perspective of patient out-of-pocket costs. The list price range of RA biologics ranges from \$5,000 to \$8,000+ per dose, and patient cost-sharing varies depending on their plan type. These drugs are typically placed on specialty tiers with either co-insurance or higher co-pays. For those paying co-insurance, costs can reach into the thousands for one fill. Many patients with commercial insurance rely on some sort of copay assistance to help afford their cost-sharing, which can cause significant problems when they enroll in Medicare and learn they can no longer use manufacturer assistance. One of the top reasons patients call our Helpline is because they have enrolled in Medicare and are having difficulty affording their cost-sharing. ..In a 2019 Arthritis Foundation survey, 40% of Medicare Part D enrollees reported that they could not access the drugs they need to manage their disease; 19% of Medicare respondents had to switch from Part D to Part B due to out-of-pocket costs. That same year we highlighted a patient story from advocate [REDACTED] who had to transitioned to a physician-administered drug because she couldn't afford the 40% co-insurance for her Part D drug. Unfortunately, she experienced negative side effects and ultimately a worsening of her disease. This is one of many stories we heard as we connected with patients on their Medicare experiences at that time. ..In a survey the AF conducted in 2021, out-of-pocket costs were cited as one of the top three barriers to accessing care. 37% of those surveyed have had trouble affording their out-of-pocket costs this past year. Of those, 54% say they have incurred debt or suffered financial hardship because of it. Similar to overly burdensome utilization management, out-of-reach costs can lead to non-adherence which results in myriad negative impacts to health. In our survey, trouble affording out-of-pocket medical expenses had negative impacts on care: 45% delayed refilling a prescription, 41% say their health care worsened, and 41% switched medications as a result.</p> <p>N</p>

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Question	Sub-Question	Response
	What type of Evidence is shown?	
Question 29: Comparative Effectiveness on Specific Populations	Response to Question 29	<p>While arthritis can impact anyone regardless of age, gender expression, race, or socioeconomic status, research indicates that African American/Black individuals, Hispanic/Latinx individuals, Asian individuals, low-income individuals, and those living in rural areas may be disproportionately impacted by arthritis-related limitations. Such limitations affect individuals' ability to work and participate in daily living – issues compounded by systemic barriers to accessing diagnosis, treatment, and support. Examples of different outcomes among disadvantaged groups include:</p> <ul style="list-style-type: none">• Black Americans with rheumatoid arthritis are less likely to receive a biologic, more likely to use glucocorticoids, and more likely to visit the emergency department than white Americans• Individuals with rheumatoid arthritis from communities of color in the US tend to have more pain, increased disability, and worse overall outcomes• Non-white individuals in the US with rheumatoid arthritis tend to experience treatment delays• Arthritis-attributable activity limitations and severe joint pain are higher for non-Hispanic Blacks, Hispanics, and multiracial or other respondents with arthritis than non-Hispanic whites with arthritis
	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?	N
	What type of Evidence is shown?	

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Question	Sub-Question	Response
Question 30: Addressing Unmet Medical Needs	Response to Question 30	Enbrel meets an important unmet need in the rheumatoid arthritis patient population because it is often prescribed for patients who have not achieved disease control when taking methotrexate alone. According the ACR clinical practice guidelines, the addition of a biological disease modifying antirheumatic drug such as Enbrel is conditionally recommended over therapy with over triple therapy (i.e., addition of sulfasalazine and hydroxychloroquine) for patients taking maximally tolerated doses of methotrexate who are not at target. For most rheumatoid arthritis patients, the first biologic they will take will be a TNF inhibitor such as Enbrel.
	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?	N
	What type of Evidence is shown?	
Question 31: Patient and Caregiver Experience	Response to Question 31	
Question 32: Executive Summary	Response to Question 32	The Arthritis Foundation polled a network of our patient advocates and aggregated their responses below...What is your experience taking the selected drug and/or its therapeutic alternative(s)? How long have you been taking the selected drug and/or its therapeutic alternative(s)?..“Enbrel was my very first biologic. Before Enbrel, I could not get down on the ground and get up. I also could not open a water bottle. About 2 months into taking Enbrel I was able to play on the ground with a toddler and then get up without assistance. I also regained the use of both hands. I took Enbrel for 2 years with good results, until I was taken off of it for foot surgery and when restarting, it stopped working.”..“Enbrel, for 23 years. Enbrel changed my life! Before Enbrel, I was having surgery every year or two, one included a shoulder replacement at 33 y.o. Generally, I have little to no inflammation and I have had no need for joint surgery since taking it.”..“I had Enbrel injections for many years with good pain control and no side effects. Had to switch to another biologic when I went on

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Question Sub-Question



Response

Medicare.”..How did treatment with the selected drug and/or its therapeutic alternative(s) impact your health, including your symptoms?..“It helped me regain mobility which is important for a retail store manager.”..“Health greatly increased as I am able to walk and exercise.”..“Very effective.”..Please describe any side effects that you have experienced, and the impact of these side effects have had on you..“I had very little side effects with this medication”..“None”.. “No side effects”..How did treatment with the selected drug and/or its therapeutic alternative(s) impact your quality of life and wellbeing?..“Physical ailments take a toll on your mental well-being, so having better physical health has greatly improved my quality of life because my physical symptoms greatly decreased. When I overdo it, I feel bad for a few days and it makes me remember how bad it used to be.”.. “Good quality of life”..Have you had challenges accessing or taking the drug? For example, challenges affording the drug, gaining coverage through your health insurance, or taking the drug as prescribed...“Had to switch to another biologic when I went on Medicare. Had side effects on the other biologic and can no longer take biologics at this time.”..As indicated throughout these comments, there is great heterogeneity in the patient experience with biologics. Many patients try two or more biologics before finding one that works for them, and at times biologics can stop working for seemingly no reason. Further, some patients have cycled through most if not all the biologics indicated for their disease, so questions about “therapeutic alternatives” will vary depending on how many alternatives are left for a given patient. Biologic therapy is vital for maintaining health and function for people living with RA, so continuous access to the biologic that works best for them is critical. We urge CMS to keep in mind these complexities throughout its process, and to place appropriate safeguards to ensure Medicare beneficiaries do not experience disruptions in care or access barriers.



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Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	ETANERCEPT
	Q26 - Respondent Name	
	Q26 - Organization Name (if applicable)	Chronic Care Policy Alliance
	Respondent Email Who is completing this form?	PAO
Question 27: Prescribing Information	Prescribing Information	<p>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.</p>
	Evidence Submitted include a cost-effectiveness measure? What type of Evidence is shown?	N
Question 28: Therapeutic Impact and Comparative Effectiveness	Therapeutic Impact and Comparative Effectiveness	<p>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.</p>

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Question	Sub-Question	Response
	<p>Hyperlink to Table/Charts/Graphs - Additional Materials for Question 28</p> <p>Evidence Submitted include a cost-effectiveness measure?</p> <p>What type of Evidence is shown?</p>	<p>N</p>
<p>Question 29: Comparative Effectiveness on Specific Populations</p>	<p>Response to Question 29</p> <p>Hyperlink to Citation - Additional Materials for Question 29</p> <p>Hyperlink to Table/Charts/Graphs - Additional Materials for Question 29</p> <p>Evidence Submitted include a cost-effectiveness measure?</p>	<p>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.</p> <p>N</p>

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Question	Sub-Question	Response
	What type of Evidence is shown?	
	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.
Question 30: Addressing Unmet Medical Needs	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?	N
	What type of Evidence is shown?	
Question 31: Patient and Caregiver Experience	Response to Question 31	
Question 32: Executive Summary	Response to Question 32	

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Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	ETANERCEPT
	Q26 - Respondent Name	
	Q26 - Organization Name (if applicable)	National Psoriasis Foundation
	Respondent Email Who is completing this form?	PAO
Question 27: Prescribing Information	Prescribing Information	No
	Evidence Submitted include a cost-effectiveness measure? What type of Evidence is shown?	N
Question 28: Therapeutic Impact and Comparative Effectiveness	Therapeutic Impact and Comparative Effectiveness	<p>The extreme heterogeneity of psoriatic disease makes physician and patient access to the full range of therapies particularly important given that a treatment that may work for one may fail for another and because patients often cycle through a number of treatments during their lifetime. Therefore, for many individuals living with psoriatic disease, therapeutic alternatives may be limited, and may require access to pharmaceuticals that may otherwise be more rare in the community. Only when physicians are able to access all the tools in their treatment toolbox will they be able to provide individual patients with the care that will maximize their health outcomes. ..New systemic treatments, including biologics like etanercept, have provided many patients with an effective therapy for the first time in their lives. In fact, today many people with psoriasis are able to achieve a level of clearance never before possible. Biologics have also opened a new world of combination therapies, being used alongside systemic treatments, phototherapy and/or topical treatments. ..It is important for patient communities to have access to a broad array of treatment options. Each patient is unique in the way they respond to therapy, and there is no 'one size fits all' approach. Stable patients should not be switched to different treatments, unless prescribed by their physician or where the alternative is a generic or biosimilar. Non-medical switching or payer mandated switching of patients can be dangerous because it exposes the patient to the risk of disease progression or return, and the patient may not be able to return to the treatment that was working for them without experiencing a loss of response. Switching patients may destabilize their health, and patients may develop immunogenicity to the treatment</p>

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Question	Sub-Question	Response
	<p>Hyperlink to Table/Charts/Graphs - Additional Materials for Question 28</p> <p>Evidence Submitted include a cost-effectiveness measure?</p> <p>What type of Evidence is shown?</p>	<p>that was working for them. It is critical to ensure the treating physician and patient are informed of any switches with ample time to appeal as necessary. Stable patients should not be exposed to increased drug cost sharing because they were unwilling to switch treatments. ..In a recent meta-analysis, etanercept was reported to be inferior on the basis of PASI-90 at 16 weeks to seven other therapeutics (Armstrong 2020), suggesting that while the therapeutic selected for negotiation by CMS retains a clinical role in the treatment of psoriatic disease, it may not be associated with best outcomes. With respect to the position of the negotiated therapies, this data has been replicated in a systematic review of 179 studies in which the authors concluded that infliximab, bimekizumab, ixekizumab, and risankizumab represented the most effective options for achieving PASI-90 in moderate to severe psoriasis. (Sbidian, 2023). Further data support that ixekizumab and risankizumab are most associated with durable positive outcomes at 1 year, specifically PASI-100 and PASI-90 (Blauvelt 2022). Additional data favor risankizumab, guselkumab, brodalumab and ixekizumab for lower number to treat relative to PASI goals (Leonardi, 2022). ..Although population level data may not favor etanercept in typical cases, it may still have an important role in individual circumstances (see question 29). Thus, the NPF position is that all therapeutic decisions should be made by a patient's health care provider in the context of the patients individual needs, and that therapies prescribed for a patient should be accessible to the patient. It should, however, be acknowledged that the most recent data, as provided above, suggest that as a population CMS should consider that any economic pressure that favors etanercept, may be associated with less therapeutic potential, and thus place CMS at risk for health care costs related to the unmet therapeutic needs.</p> <p>N</p>
Question 29: Comparative Effectiveness on Specific Populations	Response to Question 29	<p>The NPF is concerned that IRA implementation and Medicare negotiations could severely impact care for those most in need. For example, formulary design may change, which could lead to utilization management protocols that destabilize patients with ongoing treatment or further delay access to needed prescriptions. This has the possibility of impacting specific populations, including: ..Rural populations: .- Utilization management, including step protocols and switching stable patients can affect individuals in rural areas disproportionately because these practices frequently result in the need for the individual to see their doctor or medical team</p>

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Question	Sub-Question	Response
	<p data-bbox="262 950 556 1047">Hyperlink to Citation - Additional Materials for Question 29</p> <p data-bbox="262 1226 556 1356">Hyperlink to Table/Charts/Graphs - Additional Materials for Question 29</p> <p data-bbox="262 1421 598 1518">Evidence Submitted include a cost-effectiveness measure?</p>	<p data-bbox="619 251 1967 820">more frequently. .- Less access to internet may impede a patient's ability to appeal an adverse coverage determination. .- Less access to specialty practices may impact whether the physician pursues an appeal of an adverse coverage determination. ..Underserved, marginalized and poorer communities: .- Patients with less voice and fewer resources, such as underserved, marginalized, poorer individuals, and individuals who rely on others for advocacy, may be more at risk for delays in getting their medications (Chandra 2023). .- Resource poor areas may offer less access to specialty practices which impacts whether the patient has a provider with the additional staff needed to pursue an appeal of an adverse coverage determination (Winter 2019)..- Less education exacerbates health disparities because the individual would have a harder time navigating the appeals process. .- Less access to internet may impede a patient's ability to appeal an adverse coverage determination. .. Pediatric populations.- Etanercept remains recommended in relevant guidelines for treatment of pediatric psoriasis. The Joint American Academy of Dermatology and National Psoriasis Foundation guidelines for management and treatment of pediatric psoriasis support usage etanercept in pediatric populations, citing level I evidence (Menter 2020). ..Comorbid immune disorders .- Patients with inflammatory bowel disease may respond favorably to drugs such as infliximab, adalimumab, and ustekinumab which can be effective for IBD in addition to psoriasis. Other drugs, such as etanercept and anti IL-17 therapies, are only recommended with caution as they may aggravate the IBD (Whitlock 2018). Whitlock SM, Enos CW, Armstrong AW, Gottlieb A, Langley RG, Lebwohl M, Merola JF, Ryan C, Siegel MP, Weinberg JM, Wu JJ, Van Voorhees AS. Management of psoriasis in patients with inflammatory bowel disease: From the Medical Board of the National Psoriasis Foundation. J Am Acad Dermatol. 2018 Feb;78(2):383-394. doi: 10.1016/j.jaad.2017.06.043. PMID: 29332708. Chandra, Amitabh, and Benedic Ippolito. "What Does the Inflation Reduction Act Mean for Patients and Physicians?" NEJM Catalyst Innovations in Care Delivery, vol. 4, no. 10, 20 Sept. 2023, https://doi.org/10.1056/cat.23.0138. Accessed 3 Oct. 2023. Association of Black Cardiologists, Inc. "Identifying How Prior Authorization Impacts Treatment of Underserves and Minority Patients," (Winter 2019) Available at: http://abcario.org/wp-content/uploads/2019/03/AB-20190227-PA-White-Paper-Survey-Results-final.pdf</p>

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Question	Sub-Question	Response
	What type of Evidence is shown?	
Question 30: Addressing Unmet Medical Needs	Response to Question 30	<p>We would like to reemphasize our answer to question 28: The extreme heterogeneity of psoriatic disease makes physician and patient access to the full range of therapies particularly important given that a treatment that may work for one may fail for another and because patients often cycle through a number of treatments during their lifetime. Therefore, for many individuals living with psoriatic disease, therapeutic alternatives may be limited, and may require access to pharmaceuticals that may otherwise be more rare in the community. Only when physicians are able to access all the tools in their treatment toolbox will they be able to provide individual patients with the care that will maximize their health outcomes.</p>
	Hyperlink to Citation - Additional Materials for Question 30	<p>Leonardi CL, See K, Burge R, Sun Z, Zhang Y, Mallbris L, Garrelts A, Warren RB. Number Needed to Treat Network Meta-Analysis to Compare Biologic Drugs for Moderate-to-Severe Psoriasis. <i>Adv Ther.</i> 2022 May;39(5):2256-2269. doi: 10.1007/s12325-022-02065-w. Epub 2022 Mar 22. PMID: 35316500; PMCID: PMC9056462.</p> <p>Armstrong, April W et al. "Comparison of Biologics and Oral Treatments for Plaque Psoriasis: A Meta-analysis." <i>JAMA dermatology</i> vol. 156,3 (2020): 258-269. doi:10.1001/jamadermatol.2019.4029</p> <p>2. Sbidian E, Chaimani A, Guelimi R, Garcia-Doval I, Hua C, Hughes C, Naldi L, Kinberger M, Afach S, Le Cleach L. Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. <i>Cochrane Database Syst Rev.</i> 2023 Jul 12;7(7):CD011</p> <p>3. Blauvelt A, Gooderham M, Griffiths CEM, Armstrong AW, Zhu B, Burge R, Gallo G, Guo J, Garrelts A, Lebwohl M. Cumulative Clinical Benefits of Biologics in the Treatment of Patients with Moderate-to-Severe Psoriasis over 1 Year: a Network Meta-Analysis. <i>Dermatol Ther (Heidelb).</i> 2022 Mar;12(3):727-740. doi: 10.1007/s13555-022-00690-5. Epub 2022 Feb 23. PMID: 35195887; PMCID: PMC8941028.</p>
	Hyperlink to Table/Charts/Graphs - Additional Materials for Question 30	
	Evidence Submitted include a cost-effectiveness measure?	N
	What type of Evidence is shown?	

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Question	Sub-Question	Response
Question 31: Patient and Caregiver Experience	Response to Question 31	
Question 32: Executive Summary	Response to Question 32	<p>The extreme heterogeneity of this disease makes physician and patient access to the full range of therapies particularly important given that a treatment that may work for one may fail for another and because patients often cycle through a number of treatments during their lifetime. Only when physicians are able to access all the tools in their treatment toolbox will they be able to provide individual patients with the care that will maximize their health outcomes. ..While the goal of reducing costs to the healthcare system is laudable, we caution CMS to be on guard against creating environments in which prescribing behaviors are influenced inappropriately by reimbursement, which may itself be indirectly a function of drug pricing. The pharmaceutical agents under CMS review have a strong history in the management of psoriatic disease. The NPF position is that they should neither be incentivized for prescription based on cost alone, nor eliminated from the list of approved therapies available to our patient community. There is, however, a danger that lower pricing of etanercept could result in non-medical switching/payer mandated switching including fail first policies. Recent systematic reviews assess etanercept with lower likelihood of achieving satisfactory or durable PASI scores than other available therapies. Given this, CMS should further consider whether changes in prescribing habits might be associated with less favorable disease management, and thus negate the apparent savings conferred by negotiation. ..On behalf of National Psoriasis Foundation, thank you for your consideration of these comments which we hope will positively inform this review. We invite you to call upon us, our Medical Board, and our patient community as you move forward.</p>



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Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	ETANERCEPT
	Q26 - Respondent Name	
	Q26 - Organization Name (if applicable)	Pharmaceutical Care Management Association (PCMA)
	Respondent Email Who is completing this form?	TRD
Question 27: Prescribing Information	Prescribing Information	
	Evidence Submitted include a cost-effectiveness measure? What type of Evidence is shown?	
Question 28: Therapeutic Impact and Comparative Effectiveness	Therapeutic Impact and Comparative Effectiveness	<p>The Pharmaceutical Care Management Association (PCMA) appreciates the opportunity to submit comments regarding the therapeutic alternatives for Etanercept. 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</p>

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Response

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 definitional term. At the very least, aligning

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Question Sub-Question

Response

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&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 formulary design, coverage

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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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Question	Sub-Question	Response
	<p data-bbox="262 435 609 678">Hyperlink to Table/Charts/Graphs - Additional Materials for Question 28 Evidence Submitted include a cost-effectiveness measure?</p> <p data-bbox="262 719 609 784">What type of Evidence is shown?</p>	<p data-bbox="609 251 1967 427">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.</p>
<p data-bbox="63 1109 262 1279">Question 29: Comparative Effectiveness on Specific Populations</p>	<p data-bbox="262 849 609 881">Response to Question 29</p> <p data-bbox="262 954 609 1052">Hyperlink to Citation - Additional Materials for Question 29</p> <p data-bbox="262 1166 609 1295">Hyperlink to Table/Charts/Graphs - Additional Materials for Question 29</p> <p data-bbox="262 1352 609 1450">Evidence Submitted include a cost-effectiveness measure?</p> <p data-bbox="262 1482 609 1547">What type of Evidence is shown?</p>	

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Question	Sub-Question	Response
Question 30: Addressing Unmet Medical Needs	Response to Question 30 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? What type of Evidence is shown?	
Question 31: Patient and Caregiver Experience	Response to Question 31	
Question 32: Executive 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 Etanercept. 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.¹ 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

¹ 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.² 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.³ 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.⁴ 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

² *Id.* at §

³ § 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.").

⁴ 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.⁵ 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,⁶ and CMS's interpretation worryingly suggests that such coverage may also involve a preferred status designation.⁷ 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

⁵ See 42 C.F.R. § 423.128(d)(4)(ii).

⁶ Social Security Act § 1860D-4(b)(3)(I).

⁷ 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).⁸ The monthly Explanation of Benefits (EOB) must include lower cost alternatives.⁹

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."¹⁰ 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.

⁸ § 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).

⁹ 42 C.F.R. 423.138(e)(5).

¹⁰ 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.