

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

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: Bristol Myers Squibb
Drug: Eliquis (Apixaban)
<p>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:</p> <ul style="list-style-type: none"> 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. <p>The Primary Manufacturer is responsible for aggregating and reporting all necessary data on its selected drug(s) from other parties, as applicable.</p> <p>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.</p>

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

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

C. Research and Development Cost							
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.							
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

BMS has filed a lawsuit challenging the Drug Price Negotiation Program, Bristol Myers Squibb Company. v. Becerra et al., No. 3:23-03335 (D.N.J.). As alleged in the complaint BMS filed in that suit (BMS Complaint), BMS does not agree, and its signature to the “Agreement” should not be construed as implying agreement, with the characterizations, express or implied, in such “Agreement” or that any resulting price of the so-called

negotiation is "fair." BMS reserves all of its rights with respect to the Drug Price Negotiation Program, including the legal claims presented in the BMS Complaint." " BMS acquired DuPont Pharmaceuticals Company on October 1, 2001, for cash of \$7.8 billion. [REDACTED]

[REDACTED] The information provided in Section I (Evidence About Alternative Treatments) provides a more appropriate basis than acquisition costs for determining the offer and counteroffer because the Evidence About Alternative Treatments better reflects the clinical attributes of Eliquis and evidence of its benefits to patients, the healthcare system, and society. This response contains confidential, proprietary, and trade secret information that is exempt from disclosure under the Inflation Reduction Act (Social Security Act § 1193(c)), Freedom of Information Act Exemption 4 (5 U.S.C. § 552(b)(4)), and the Trade Secrets Act (18 U.S.C. § 1905).

Explanation of Basic Pre-Clinical Research Costs

[REDACTED]

The information provided in Section I (Evidence About Alternative Treatments) provides a more appropriate basis than R&D costs for determining the offer and counteroffer because the Evidence About Alternative Treatments better reflects the clinical attributes of Eliquis and evidence of its benefits to patients, the healthcare system, and society. This response contains confidential, proprietary, and trade secret information that is exempt from disclosure under the Inflation Reduction Act (Social Security Act § 1193(c)), Freedom of Information Act Exemption 4 (5 U.S.C. § 552(b)(4)), and the Trade Secrets Act (18 U.S.C. § 1905).

Explanation of Post-IND Costs

[REDACTED] Accordingly, the value above does not provide a complete picture of the post-IND costs incurred by BMS in developing all approved indications of Eliquis. [REDACTED]

[REDACTED]

The post-IND period began on November 28, 2002, the day the IND application for the first FDA-approved indication of Eliquis went into effect. The post-IND period has not ended because BMS has a remaining requirement for a post marketing trial under the Pediatric Research Equity Act.

[REDACTED] BMS asks that in calculating recoupment or adjusting the preliminary price, CMS take into consideration the fact that the available R&D cost data do not fully reflect total R&D costs incurred by BMS for all FDA-approved indications of Eliquis.

[REDACTED]

[REDACTED] Costs are shared between BMS and Pfizer under the alliance agreement at approximately an equal share to the two parties where on a quarterly basis both parties record allowable R&D expenses incurred by each party and split the total approximately equally in accordance with the alliance agreement. [REDACTED]

[REDACTED]

Global study costs to support U.S filing for FDA approval were included. Studies conducted to support approval in specific non-U.S. countries were excluded. [REDACTED]

[REDACTED]

The costs included in this response are for all FDA-approved indications. [REDACTED]

[REDACTED]

In terms of R&D tax credits applied, no credit was deducted from the above. For additional details, see Question 10 text response field.

[REDACTED]

The methodology used is consistent with our accounting policies and generally accepted accounting principles in the United States. A cost of capital was not used to adjust the figures in this response [REDACTED]

[REDACTED] Additionally, no adjustments were made for inflation in accordance with the instructions for reporting monetary amounts.

Eliquis did not receive accelerated approval and therefore no additional costs for post-approval confirmatory studies were incurred. [REDACTED]

[REDACTED]

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

[REDACTED]

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Explanation of Costs of Other R&D

[REDACTED]

The amount above represents post-marketing data generation study costs that were not FDA-required or were FDA-required and not yet completed. [REDACTED]

The information provided in Section I (Evidence About Alternative Treatments) provides a more appropriate basis than R&D costs for determining the offer and counteroffer because the Evidence About Alternative Treatments better reflects the clinical attributes of Eliquis and evidence of its benefits to patients, the healthcare system, and society.

[REDACTED] This response contains confidential, proprietary, and trade secret information that is exempt from disclosure under the Inflation Reduction Act (Social Security Act § 1193(c)), Freedom of Information Act Exemption 4 (5 U.S.C. § 552(b)(4)), and the Trade Secrets Act (18 U.S.C. § 1905).

Explanation of Global Lifetime Net Revenue

Global, Lifetime Net Revenue of Eliquis includes adjusted gross sales of the product from ex-U.S. launch in 2012 through June 30, 2023, minus deductions for chargebacks; Medicare, Medicaid, and managed care rebates; U.S. Coverage GAP payments to CMS; early prompt pay cash discounts; sales returns; and co-pay coupons. Adjustments to Global, Lifetime Net Revenue of Eliquis DO NOT include quarterly profit-sharing payments to Pfizer [REDACTED] on global net sales of Eliquis. [REDACTED]

This data that CMS has requested omits key information that is relevant to understanding a more complete picture of our investments in innovation and our product lifecycle (e.g., the data limits failed and abandoned R&D costs to only the same mechanism of action/active ingredient/therapeutic class as the selected drug, mixes U.S. and ex-U.S. data in a complex and incomplete portrayal of our business, excludes commercialization costs, etc.). [REDACTED]

The information provided in Section I (Evidence About Alternative Treatments) provides a more appropriate basis than revenue data for determining the offer and counteroffer because the Evidence About Alternative Treatments better reflects the clinical attributes of Eliquis and

evidence of its benefits to patients, the healthcare system, and society. This response contains confidential, proprietary, and trade secret information that is exempt from disclosure under the Inflation Reduction Act (Social Security Act § 1193(c)), Freedom of Information Act Exemption 4 (5 U.S.C. § 552(b)(4)), and the Trade Secrets Act (18 U.S.C. § 1905).

Explanation of U.S. Lifetime Net Revenue

U.S. Lifetime Net Revenue of Eliquis includes adjusted gross sales of the product from U.S. launch in 2013 through June 30, 2023, minus deductions for chargebacks; Medicare, Medicaid, and managed care rebates; U.S. Coverage GAP payments to CMS; early prompt pay cash discounts; sales returns; and co-pay coupons. [REDACTED]

This data that CMS has requested omits key information that is relevant to understanding a more complete picture of our investments in innovation and our product lifecycle (e.g., the data limits failed and abandoned R&D costs to only the same mechanism of action/active ingredient/therapeutic class as the selected drug, mixes U.S. and ex-U.S. data in a complex and incomplete portrayal of our business, excludes commercialization costs, etc.). [REDACTED]

The information provided in Section I (Evidence About Alternative Treatments) provides a more appropriate basis than revenue data for determining the offer and counteroffer because the Evidence About Alternative Treatments better reflects the clinical attributes of Eliquis and evidence of its benefits to patients, the healthcare system, and society. This response contains confidential, proprietary, and trade secret information that is exempt from disclosure under the Inflation Reduction Act (Social Security Act § 1193(c)), Freedom of Information Act Exemption 4 (5 U.S.C. § 552(b)(4)), and the Trade Secrets Act (18 U.S.C. § 1905).

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
00003-0893-21			EA	
00003-0893-31			EA	
00003-0894-21			EA	
00003-0894-31			EA	
00003-3764-74			EA	
00003-0894-70			EA	

Explanations: (Note: The system only allowed two decimal places for Average Distribution Costs. The Average Distribution Costs by NDC are as follows:

[REDACTED]

[REDACTED]

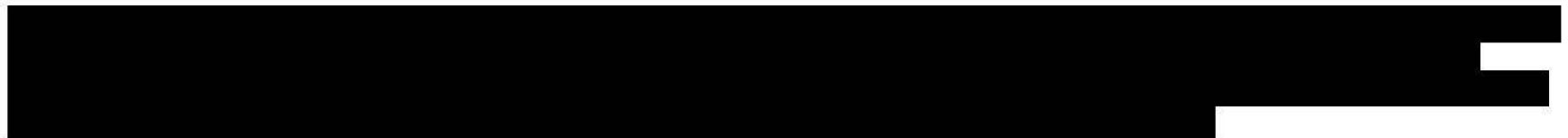
The information provided in Section I (Evidence About Alternative Treatments) provides a more appropriate basis than unit costs of production and distribution for determining the offer and counteroffer because the Evidence About Alternative Treatments better reflects the clinical attributes of Eliquis and evidence of its benefits to patients, the healthcare system, and society. This response contains confidential, proprietary, and trade secret information that is exempt from disclosure under the Inflation Reduction Act (Social Security Act § 1193(c)), Freedom of Information Act Exemption 4 (5 U.S.C. § 552(b)(4)), and the Trade Secrets Act (18 U.S.C. § 1905).

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
\$ -	(refer to Explanations)	OTH		

Explanations:

Federal Financial Support

Identification Number for Grants and Comparable Awards: N/A



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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
US 6,413,980	1999-12-22	2019-12-22	Y	Y	Y	N	UTL	Y
US 6,919,451	2002-12-03	2013-08-19	N	N	N	N	UTL	N
US 6,967,208	2002-09-17	2026-11-21	Y	Y	Y	N	UTL	Y
US 7,396,932	2005-09-26	2026-10-10	N	N	N	N	UTL	N
US 9,326,945	2011-02-24	2031-02-24	Y	N	N	N	UTL	Y
US 9,452,134	2013-09-26	2033-09-26	N	N	N	N	UTL	N
US 10,016,362	2013-09-26	2033-09-26	N	N	N	N	UTL	N
U.S. Patent Application No. 17/047,428 (U.S. Publication No. US2021/0145817A1)	2019-04-15	9999-12-31	N	N	N	Y	UTL	N

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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

Explanations: The Orange Book currently lists two U.S. patents for Eliquis: (1) US 6,967,208, entitled "Lactam-Containing Compounds and Derivatives Thereof As Factor Xa Inhibitors"; and (2) US 9,326,945, entitled "Apixiban Formulations."

For US 6,967,208, the Patent Use Codes listed in the Orange Book regarding the 2.5 mg tablet are U-1167, U-1200, U-1301, U-1302, U-1323, U-1501, U-1502, U-1729, and U-1730.


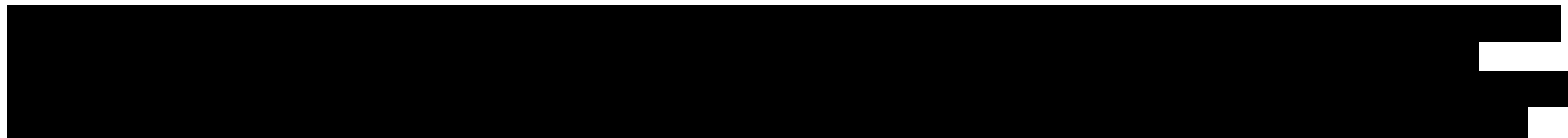
For US 6,967,208, the Patent Use Codes listed in the Orange Book regarding the 5 mg tablet are U-1200, U-1301, U-1302, and U-1323. A description of these use codes can be found on FDA's website: https://www.accessdata.fda.gov/scripts/cder/ob/results_patent.cfm.

A third U.S. patent, US 6,413,980, entitled "Nitrogen Containing Heterobicycles As Factor Xa Inhibitors," is not currently listed in the Orange Book since it has expired, but was previously listed in conjunction with Patent Use Codes U-1200, U-1301, U-1302, and U-1501.



There are two process-related patents, which are not listed/listable in the Orange Book:

- (1) US 6,919,451, entitled "Synthesis of 4,5-dihydro-pyrazolo[3,4-C]pyrid-2-ones"; and
- (2) US 7,396,932, entitled "Process for Preparing 4,5-dihydro-pyrazolo[3,4-C]Pyrid-2-ones".

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- (1) US 9,452,134, entitled "Apixaban Solution Formulations," is not listed in the Orange Book for Eliquis.
 - (2) US 10,016,362, entitled "Apixaban Solution Formulations," is not listed in the Orange Book for Eliquis.
 - (3) US Patent Application No. 17/047,428 (US Publication No. US2021/0145817A1), entitled "Apixaban Formulations," is pending at the U.S. Patent & Trademark Office, and thus it does not have a definitive patent expiry date. We have filled in 12/31/9999 in the expiration date field per CMS instructions.
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[REDACTED]

[REDACTED]

[REDACTED]

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
CEE	2017-12-28	202155	00003-0893, 00003-0894, 00003-3764	[REDACTED]

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
CIE	2017-03-03	202155	00003-0893, 00003-0894	New Clinical Investigation exclusivity with FDA Code I-681: "Prophylaxis of deep vein thrombosis (DVT) which may lead to pulmonary embolism (PE), in adult patients who have undergone hip or knee replacement."
CIE	2017-08-21	202155	00003-0893, 00003-0894	New Clinical Investigation exclusivity with FDA Code I-661: "Treatment of pulmonary embolism."
CIE	2017-08-21	202155	00003-0893, 00003-0894	New Clinical Investigation exclusivity with FDA Code I-690: "Indicated for the treatment of deep vein thrombosis (DVT)."
CIE	2017-08-21	202155	00003-0893, 00003-0894	New Clinical Investigation exclusivity with FDA Code I-691: "Indicated to reduce the risk of recurrent deep vein thrombosis (DVT) and pulmonary embolism (PE) following initial therapy."

Explanations: None.

F. Patents, Exclusivities, and Approvals								
All Active and Pending FDA Applications and Approvals								
Description: Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. This list contains all active and pending FDA applications and approvals for the selected drug under section 505(c) of the FD&C Act and 351(a) of the PHS Act.								
Application (NDA / BLA) Number	Application Type (NDA; BLA)	Class Code	Approval Date	Indication	Dosage Form and Strength	Sponsor	Application Status	Comments
202155	NDA	1	2012-12-28	To reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation	2.5 and 5 mg tablets	Bristol-Myers Squibb	APP	
202155003	NDA	1	2014-03-13	For the prophylaxis of deep vein thrombosis (DVT) which may lead to pulmonary embolism (PE), in adult	2.5 and 5 mg tablets	Bristol-Myers Squibb	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
				patients who have undergone hip or knee replacement surgery				
202155006	NDA	1	2014-08-21	For the treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE), and for the reduction in the risk of recurrent DVT and PE	2.5 and 5 mg tablets	Bristol-Myers Squibb	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
				following initial therapy				

Explanations:

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
00003-0893-21	2023-Q2	\$ 9.35	EA	
00003-0893-21	2023-Q1	\$ 9.35	EA	
00003-0893-21	2022-Q4	\$ 8.82	EA	
00003-0893-21	2022-Q3	\$ 8.82	EA	
00003-0893-21	2022-Q2	\$ 8.82	EA	
00003-0893-21	2022-Q1	\$ 8.82	EA	
00003-0893-21	2021-Q4	\$ 8.32	EA	
00003-0893-21	2021-Q3	\$ 8.32	EA	
00003-0893-21	2021-Q2	\$ 8.32	EA	
00003-0893-21	2021-Q1	\$ 8.32	EA	
00003-0893-21	2020-Q4	\$ 7.85	EA	
00003-0893-21	2020-Q3	\$ 7.85	EA	
00003-0893-21	2020-Q2	\$ 7.85	EA	
00003-0893-21	2020-Q1	\$ 7.85	EA	
00003-0893-21	2019-Q4	\$ 7.40	EA	
00003-0893-21	2019-Q3	\$ 7.40	EA	
00003-0893-21	2019-Q2	\$ 7.40	EA	
00003-0893-21	2019-Q1	\$ 7.40	EA	
00003-0893-21	2018-Q4	\$ 6.98	EA	
00003-0893-21	2018-Q3	\$ 6.98	EA	
00003-0893-31	2023-Q2	\$ 9.35	EA	
00003-0893-31	2023-Q1	\$ 9.35	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
00003-0893-31	2022-Q4	\$ 8.82	EA	
00003-0893-31	2022-Q3	\$ 8.82	EA	
00003-0893-31	2022-Q2	\$ 8.82	EA	
00003-0893-31	2022-Q1	\$ 8.82	EA	
00003-0893-31	2021-Q4	\$ 8.32	EA	
00003-0893-31	2021-Q3	\$ 8.32	EA	
00003-0893-31	2021-Q2	\$ 8.32	EA	
00003-0893-31	2021-Q1	\$ 8.32	EA	
00003-0893-31	2020-Q4	\$ 7.85	EA	
00003-0893-31	2020-Q3	\$ 7.85	EA	
00003-0893-31	2020-Q2	\$ 7.85	EA	
00003-0893-31	2020-Q1	\$ 7.85	EA	
00003-0893-31	2019-Q4	\$ 7.40	EA	
00003-0893-31	2019-Q3	\$ 7.40	EA	
00003-0893-31	2019-Q2	\$ 7.40	EA	
00003-0893-31	2019-Q1	\$ 7.40	EA	
00003-0893-31	2018-Q4	\$ 6.98	EA	
00003-0893-31	2018-Q3	\$ 6.98	EA	
00003-0894-21	2023-Q2	\$ 9.35	EA	
00003-0894-21	2023-Q1	\$ 9.35	EA	
00003-0894-21	2022-Q4	\$ 8.82	EA	
00003-0894-21	2022-Q3	\$ 8.82	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
00003-0894-21	2022-Q2	\$ 8.82	EA	
00003-0894-21	2022-Q1	\$ 8.82	EA	
00003-0894-21	2021-Q4	\$ 8.32	EA	
00003-0894-21	2021-Q3	\$ 8.32	EA	
00003-0894-21	2021-Q2	\$ 8.32	EA	
00003-0894-21	2021-Q1	\$ 8.32	EA	
00003-0894-21	2020-Q4	\$ 7.85	EA	
00003-0894-21	2020-Q3	\$ 7.85	EA	
00003-0894-21	2020-Q2	\$ 7.85	EA	
00003-0894-21	2020-Q1	\$ 7.85	EA	
00003-0894-21	2019-Q4	\$ 7.40	EA	
00003-0894-21	2019-Q3	\$ 7.40	EA	
00003-0894-21	2019-Q2	\$ 7.40	EA	
00003-0894-21	2019-Q1	\$ 7.40	EA	
00003-0894-21	2018-Q4	\$ 6.98	EA	
00003-0894-21	2018-Q3	\$ 6.98	EA	
00003-0894-31	2023-Q2	\$ 9.35	EA	
00003-0894-31	2023-Q1	\$ 9.35	EA	
00003-0894-31	2022-Q4	\$ 8.82	EA	
00003-0894-31	2022-Q3	\$ 8.82	EA	
00003-0894-31	2022-Q2	\$ 8.82	EA	
00003-0894-31	2022-Q1	\$ 8.82	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
00003-0894-31	2021-Q4	\$ 8.32	EA	
00003-0894-31	2021-Q3	\$ 8.32	EA	
00003-0894-31	2021-Q2	\$ 8.32	EA	
00003-0894-31	2021-Q1	\$ 8.32	EA	
00003-0894-31	2020-Q4	\$ 7.85	EA	
00003-0894-31	2020-Q3	\$ 7.85	EA	
00003-0894-31	2020-Q2	\$ 7.85	EA	
00003-0894-31	2020-Q1	\$ 7.85	EA	
00003-0894-31	2019-Q4	\$ 7.40	EA	
00003-0894-31	2019-Q3	\$ 7.40	EA	
00003-0894-31	2019-Q2	\$ 7.40	EA	
00003-0894-31	2019-Q1	\$ 7.40	EA	
00003-0894-31	2018-Q4	\$ 6.98	EA	
00003-0894-31	2018-Q3	\$ 6.98	EA	
00003-0894-70	2023-Q2	\$ 9.35	EA	
00003-0894-70	2023-Q1	\$ 9.35	EA	
00003-0894-70	2022-Q4	\$ 8.82	EA	
00003-0894-70	2022-Q3	\$ 8.82	EA	
00003-0894-70	2022-Q2	\$ 8.82	EA	
00003-0894-70	2022-Q1	\$ 8.82	EA	
00003-0894-70	2021-Q4	\$ 8.32	EA	
00003-0894-70	2021-Q3	\$ 8.32	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
00003-0894-70	2021-Q2	\$ 8.32	EA	
00003-0894-70	2021-Q1	\$ 8.32	EA	
00003-0894-70	2020-Q4	\$ 7.85	EA	
00003-0894-70	2020-Q3	\$ 7.85	EA	
00003-0894-70	2020-Q2	\$ 7.85	EA	
00003-0894-70	2020-Q1	\$ 7.85	EA	
00003-0894-70	2019-Q4	\$ 7.40	EA	
00003-0894-70	2019-Q3	\$ 7.40	EA	
00003-0894-70	2019-Q2	\$ 7.40	EA	
00003-0894-70	2019-Q1	\$ 7.40	EA	
00003-0894-70	2018-Q4	\$ 6.98	EA	
00003-0894-70	2018-Q3	\$ 6.98	EA	
00003-3764-74	2023-Q2	\$ 9.35	EA	
00003-3764-74	2023-Q1	\$ 9.35	EA	
00003-3764-74	2022-Q4	\$ 8.82	EA	
00003-3764-74	2022-Q3	\$ 8.82	EA	
00003-3764-74	2022-Q2	\$ 8.82	EA	
00003-3764-74	2022-Q1	\$ 8.82	EA	
00003-3764-74	2021-Q4	\$ 8.32	EA	
00003-3764-74	2021-Q3	\$ 8.32	EA	
00003-3764-74	2021-Q2	\$ 8.32	EA	
00003-3764-74	2021-Q1	\$ 8.32	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
00003-3764-74	2020-Q4	\$ 7.85	EA	
00003-3764-74	2020-Q3	\$ 7.85	EA	
00003-3764-74	2020-Q2	\$ 7.85	EA	
00003-3764-74	2020-Q1	\$ 7.85	EA	
00003-3764-74	2019-Q4	\$ 7.40	EA	
00003-3764-74	2019-Q3	\$ 7.40	EA	
00003-3764-74	2019-Q2	\$ 7.40	EA	
00003-3764-74	2019-Q1	\$ 7.40	EA	
00003-3764-74	2018-Q4	\$ 6.98	EA	
00003-3764-74	2018-Q3	\$ 6.98	EA	

Explanations: WAC unit price data was pulled from internal systems and validated against First Databank WAC data to confirm alignment.

This response contains confidential, proprietary, and trade secret information that is exempt from disclosure under the Inflation Reduction Act (Social Security Act § 1193(c)), Freedom of Information Act Exemption 4 (5 U.S.C. § 552(b)(4)), and the Trade Secrets Act (18 U.S.C. § 1905).

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	00003-0893	2023-Q2		EA	
Y	00003-0893	2023-Q1		EA	
Y	00003-0893	2022-Q4		EA	
Y	00003-0893	2022-Q3		EA	
Y	00003-0893	2022-Q2		EA	
Y	00003-0893	2022-Q1		EA	
Y	00003-0893	2021-Q4		EA	
Y	00003-0893	2021-Q3		EA	
Y	00003-0893	2021-Q2		EA	
Y	00003-0893	2021-Q1		EA	
Y	00003-0893	2020-Q4		EA	
Y	00003-0893	2020-Q3		EA	
Y	00003-0893	2020-Q2		EA	
Y	00003-0893	2020-Q1		EA	
Y	00003-0893	2019-Q4		EA	
Y	00003-0893	2019-Q3		EA	
Y	00003-0893	2019-Q2		EA	
Y	00003-0893	2019-Q1		EA	
Y	00003-0893	2018-Q4		EA	
Y	00003-0893	2018-Q3		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	00003-0894	2023-Q2		EA	
Y	00003-0894	2023-Q1		EA	
Y	00003-0894	2022-Q4		EA	
Y	00003-0894	2022-Q3		EA	
Y	00003-0894	2022-Q2		EA	
Y	00003-0894	2022-Q1		EA	
Y	00003-0894	2021-Q4		EA	
Y	00003-0894	2021-Q3		EA	
Y	00003-0894	2021-Q2		EA	
Y	00003-0894	2021-Q1		EA	
Y	00003-0894	2020-Q4		EA	
Y	00003-0894	2020-Q3		EA	
Y	00003-0894	2020-Q2		EA	
Y	00003-0894	2020-Q1		EA	
Y	00003-0894	2019-Q4		EA	
Y	00003-0894	2019-Q3		EA	
Y	00003-0894	2019-Q2		EA	
Y	00003-0894	2019-Q1		EA	
Y	00003-0894	2018-Q4		EA	
Y	00003-0894	2018-Q3		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	00003-3764	2023-Q2		EA	
Y	00003-3764	2023-Q1		EA	
Y	00003-3764	2022-Q4		EA	
Y	00003-3764	2022-Q3		EA	
Y	00003-3764	2022-Q2		EA	
Y	00003-3764	2022-Q1		EA	
Y	00003-3764	2021-Q4		EA	
Y	00003-3764	2021-Q3		EA	
Y	00003-3764	2021-Q2		EA	
Y	00003-3764	2021-Q1		EA	
Y	00003-3764	2020-Q4		EA	
Y	00003-3764	2020-Q3		EA	
Y	00003-3764	2020-Q2		EA	
Y	00003-3764	2020-Q1		EA	
Y	00003-3764	2019-Q4		EA	
Y	00003-3764	2019-Q3		EA	
Y	00003-3764	2019-Q2		EA	
Y	00003-3764	2019-Q1		EA	
Y	00003-3764	2018-Q4		EA	
Y	00003-3764	2018-Q3		EA	

Explanations: Reflects Best Prices Reported to CMS as of September 27, 2023. The closest unit type reported for Eliquis is an “each”. For Medicaid AMP and Best Price, the unit type reported for Eliquis is a “tablet.” This response contains confidential, proprietary, and trade secret information that is exempt from disclosure under the Inflation Reduction Act (Social Security Act § 1193(c)), Freedom of Information Act Exemption 4 (5 U.S.C. § 552(b)(4)), and the Trade Secrets Act (18 U.S.C. § 1905).

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	00003-0894-21	2023-01-01 - 2023-06-30	\$1.51	EA	
Y	00003-0893-31	2023-01-01 - 2023-06-30	\$1.51	EA	
Y	00003-0894-70	2023-01-01 - 2023-06-30	\$1.51	EA	
Y	00003-3764-74	2023-01-01 - 2023-06-30	\$1.51	EA	
Y	00003-0894-31	2023-01-01 - 2023-06-30	\$1.51	EA	
Y	00003-0893-21	2023-01-01 - 2023-06-30	\$1.51	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	00003-0894-70	2022-01-01 - 2022-12-31	\$1.51	EA	
Y	00003-0894-21	2022-01-01 - 2022-12-31	\$1.51	EA	
Y	00003-0894-31	2022-01-01 - 2022-12-31	\$1.51	EA	
Y	00003-0893-21	2022-01-01 - 2022-12-31	\$1.51	EA	
Y	00003-3764-74	2022-01-01 - 2022-12-31	\$1.51	EA	
Y	00003-0893-31	2022-01-01 - 2022-12-31	\$1.51	EA	
Y	00003-0893-21	2021-01-01 - 2021-12-31	\$1.51	EA	
Y	00003-0894-31	2021-01-01 - 2021-12-31	\$1.51	EA	
Y	00003-3764-74	2021-01-01 - 2021-12-31	\$1.51	EA	
Y	00003-0893-31	2021-01-01 - 2021-12-31	\$1.51	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	00003-0894-21	2021-01-01 - 2021-12-31	\$1.51	EA	
Y	00003-0894-70	2021-01-01 - 2021-12-31	\$1.51	EA	
Y	00003-0893-21	2020-01-01 - 2020-12-31	\$1.51	EA	
Y	00003-0893-31	2020-01-01 - 2020-12-31	\$1.51	EA	
Y	00003-0894-21	2020-01-01 - 2020-12-31	\$1.51	EA	
Y	00003-0894-31	2020-01-01 - 2020-12-31	\$1.51	EA	
Y	00003-0894-70	2020-01-01 - 2020-12-31	\$1.51	EA	
Y	00003-3764-74	2020-01-01 - 2020-12-31	\$1.51	EA	
Y	00003-0893-21	2019-01-01 - 2019-12-31	\$1.51	EA	
Y	00003-0893-31	2019-01-01 - 2019-12-31	\$1.51	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	00003-0894-70	2019-01-01 - 2019-12-31	\$1.51	EA	
Y	00003-0894-21	2019-01-01 - 2019-12-31	\$1.51	EA	
Y	00003-3764-74	2019-01-01 - 2019-12-31	\$1.51	EA	
Y	00003-0894-31	2019-01-01 - 2019-12-31	\$1.51	EA	
Y	00003-0893-31	2018-07-01 - 2018-12-31	\$1.51	EA	
Y	00003-0894-70	2018-07-01 - 2018-12-31	\$1.51	EA	
Y	00003-0894-31	2018-07-01 - 2018-12-31	\$1.51	EA	
Y	00003-3764-74	2018-07-01 - 2018-12-31	\$1.51	EA	
Y	00003-0893-21	2018-07-01 - 2018-12-31	\$1.51	EA	
Y	00003-0894-21	2018-07-01 - 2018-12-31	\$1.51	EA	

Explanations: [REDACTED] Price shown is the mandated FSS price per tablet. The information provided in Section I (Evidence About Alternative Treatments) provides a more appropriate basis than market data and sales volume data for determining the offer and counteroffer because the Evidence About Alternative Treatments better reflects the clinical attributes of Eliquis and evidence of its benefits to patients, the healthcare system, and society. This response contains confidential, proprietary, and trade secret information that is exempt from disclosure under the Inflation Reduction Act (Social Security Act § 1193(c)), Freedom of Information Act Exemption 4 (5 U.S.C. § 552(b)(4)), and the Trade Secrets Act (18 U.S.C. § 1905).

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	00003-0894-70	2023-01-01 - 2023-06-30	\$1.51	EA	[REDACTED]	
Y	00003-0893-31	2023-01-01 - 2023-06-30	\$1.51	EA		
Y	00003-0894-21	2023-01-01 - 2023-06-30	\$1.51	EA		
Y	00003-0894-31	2023-01-01 - 2023-06-30	\$1.51	EA		
Y	00003-0893-21	2023-01-01 - 2023-06-30	\$1.51	EA		
Y	00003-3764-74	2023-01-01 - 2023-06-30	\$1.51	EA		
Y	00003-0893-31	2022-01-01 - 2022-12-31	\$1.51	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	00003-0894-70	2022-01-01 - 2022-12-31	\$1.51	EA	
Y	00003-0893-21	2022-01-01 - 2022-12-31	\$1.51	EA	
Y	00003-0894-31	2022-01-01 - 2022-12-31	\$1.51	EA	
Y	00003-0894-21	2022-01-01 - 2022-12-31	\$1.51	EA	
Y	00003-3764-74	2022-01-01 - 2022-12-31	\$1.51	EA	
Y	00003-0893-21	2021-01-01 - 2021-12-31	\$1.51	EA	
Y	00003-0894-31	2021-01-01 - 2021-12-31	\$1.51	EA	
Y	00003-0894-70	2021-01-01 - 2021-12-31	\$1.51	EA	
Y	00003-0893-31	2021-01-01 - 2021-12-31	\$1.51	EA	
Y	00003-3764-74	2021-01-01 - 2021-12-31	\$1.51	EA	
Y	00003-0894-21	2021-01-01 - 2021-12-31	\$1.51	EA	
Y	00003-0894-70	2020-01-01 - 2020-12-31	\$1.51	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	00003-0893-21	2020-01-01 - 2020-12-31	\$1.51	EA	
Y	00003-3764-74	2020-01-01 - 2020-12-31	\$1.51	EA	
Y	00003-0894-21	2020-01-01 - 2020-12-31	\$1.51	EA	
Y	00003-0894-31	2020-01-01 - 2020-12-31	\$1.51	EA	
Y	00003-0893-31	2020-01-01 - 2020-12-31	\$1.51	EA	
Y	00003-3764-74	2019-01-01 - 2019-12-31	\$1.51	EA	
Y	00003-0893-31	2019-01-01 - 2019-12-31	\$1.51	EA	
Y	00003-0893-21	2019-01-01 - 2019-12-31	\$1.51	EA	
Y	00003-0894-21	2019-01-01 - 2019-12-31	\$1.51	EA	
Y	00003-0894-31	2019-01-01 - 2019-12-31	\$1.51	EA	
Y	00003-0894-70	2019-01-01 - 2019-12-31	\$1.51	EA	
Y	00003-0893-21	2018-07-01 - 2018-12-31	\$1.51	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	00003-0893-31	2018-07-01 - 2018-12-31	\$1.51	EA	
Y	00003-3764-74	2018-07-01 - 2018-12-31	\$1.51	EA	
Y	00003-0894-31	2018-07-01 - 2018-12-31	\$1.51	EA	
Y	00003-0894-21	2018-07-01 - 2018-12-31	\$1.51	EA	
Y	00003-0894-70	2018-07-01 - 2018-12-31	\$1.51	EA	

Explanations:

Price shown is the mandated Big Four price per tablet.

The information provided in Section I (Evidence About Alternative Treatments) provides a more appropriate basis than market data and sales volume data for determining the offer and counteroffer because the Evidence About Alternative Treatments better reflects the clinical attributes of Eliquis and evidence of its benefits to patients, the healthcare system, and society. This response contains confidential, proprietary, and trade secret information that is exempt from disclosure under the Inflation Reduction Act (Social Security Act § 1193(c)), Freedom of Information Act Exemption 4 (5 U.S.C. § 552(b)(4)), and the Trade Secrets Act (18 U.S.C. § 1905).

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
00003-0893-21	2023-Q1				EA	
00003-0893-21	2022-Q4				EA	
00003-0893-21	2022-Q3				EA	
00003-0893-21	2022-Q2				EA	
00003-0893-21	2022-Q1				EA	
00003-0893-21	2021-Q4				EA	
00003-0893-21	2021-Q3				EA	
00003-0893-21	2021-Q2				EA	
00003-0893-21	2021-Q1				EA	
00003-0893-21	2020-Q4				EA	
00003-0893-21	2020-Q3				EA	
00003-0893-21	2020-Q2				EA	
00003-0893-21	2020-Q1				EA	
00003-0893-21	2019-Q4				EA	
00003-0893-21	2019-Q3				EA	
00003-0893-21	2019-Q2				EA	
00003-0893-21	2019-Q1				EA	
00003-0893-21	2018-Q4				EA	
00003-0893-21	2018-Q3				EA	
00003-0893-21	2018-Q2				EA	
00003-0893-31	2023-Q1				EA	
00003-0893-31	2022-Q4				EA	

G. Market Data and Revenue and Sales Volume Data

U.S. Commercial Average Net Unit Price

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

National Drug Code (NDC-11)	Quarter	U.S. Commercial Average Unit Net Price	U.S. Commercial Average Net Unit Price - Without Patient Assistance Programs	U.S. Commercial Average Net Unit Price- Best	Unit type (EA, ML, GM)	Total Unit Volume
00003-0893-31	2022-Q3				EA	
00003-0893-31	2022-Q2				EA	
00003-0893-31	2022-Q1				EA	
00003-0893-31	2021-Q4				EA	
00003-0893-31	2021-Q3				EA	
00003-0893-31	2021-Q2				EA	
00003-0893-31	2021-Q1				EA	
00003-0893-31	2020-Q4				EA	
00003-0893-31	2020-Q3				EA	
00003-0893-31	2020-Q2				EA	
00003-0893-31	2020-Q1				EA	
00003-0893-31	2019-Q4				EA	
00003-0893-31	2019-Q3				EA	
00003-0893-31	2019-Q2				EA	
00003-0893-31	2019-Q1				EA	
00003-0893-31	2018-Q4				EA	
00003-0893-31	2018-Q3				EA	
00003-0893-31	2018-Q2				EA	
00003-0894-21	2023-Q1				EA	
00003-0894-21	2022-Q4				EA	
00003-0894-21	2022-Q3				EA	
00003-0894-21	2022-Q2				EA	

G. Market Data and Revenue and Sales Volume Data

U.S. Commercial Average Net Unit Price

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

National Drug Code (NDC-11)	Quarter	U.S. Commercial Average Unit Net Price	U.S. Commercial Average Net Unit Price - Without Patient Assistance Programs	U.S. Commercial Average Net Unit Price- Best	Unit type (EA, ML, GM)	Total Unit Volume
00003-0894-21	2022-Q1				EA	
00003-0894-21	2021-Q4				EA	
00003-0894-21	2021-Q3				EA	
00003-0894-21	2021-Q2				EA	
00003-0894-21	2021-Q1				EA	
00003-0894-21	2020-Q4				EA	
00003-0894-21	2020-Q3				EA	
00003-0894-21	2020-Q2				EA	
00003-0894-21	2020-Q1				EA	
00003-0894-21	2019-Q4				EA	
00003-0894-21	2019-Q3				EA	
00003-0894-21	2019-Q2				EA	
00003-0894-21	2019-Q1				EA	
00003-0894-21	2018-Q4				EA	
00003-0894-21	2018-Q3				EA	
00003-0894-21	2018-Q2				EA	
00003-0894-31	2023-Q1				EA	
00003-0894-31	2022-Q4				EA	
00003-0894-31	2022-Q3				EA	
00003-0894-31	2022-Q2				EA	
00003-0894-31	2022-Q1				EA	
00003-0894-31	2021-Q4				EA	

G. Market Data and Revenue and Sales Volume Data

U.S. Commercial Average Net Unit Price

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

National Drug Code (NDC-11)	Quarter	U.S. Commercial Average Unit Net Price	U.S. Commercial Average Net Unit Price - Without Patient Assistance Programs	U.S. Commercial Average Net Unit Price- Best	Unit type (EA, ML, GM)	Total Unit Volume
00003-0894-31	2021-Q3				EA	
00003-0894-31	2021-Q2				EA	
00003-0894-31	2021-Q1				EA	
00003-0894-31	2020-Q4				EA	
00003-0894-31	2020-Q3				EA	
00003-0894-31	2020-Q2				EA	
00003-0894-31	2020-Q1				EA	
00003-0894-31	2019-Q4				EA	
00003-0894-31	2019-Q3				EA	
00003-0894-31	2019-Q2				EA	
00003-0894-31	2019-Q1				EA	
00003-0894-31	2018-Q4				EA	
00003-0894-31	2018-Q3				EA	
00003-0894-31	2018-Q2				EA	
00003-0894-70	2023-Q1				EA	
00003-0894-70	2022-Q4				EA	
00003-0894-70	2022-Q3				EA	
00003-0894-70	2022-Q2				EA	
00003-0894-70	2022-Q1				EA	
00003-0894-70	2021-Q4				EA	
00003-0894-70	2021-Q3				EA	
00003-0894-70	2021-Q2				EA	

G. Market Data and Revenue and Sales Volume Data

U.S. Commercial Average Net Unit Price

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

National Drug Code (NDC-11)	Quarter	U.S. Commercial Average Unit Net Price	U.S. Commercial Average Net Unit Price - Without Patient Assistance Programs	U.S. Commercial Average Net Unit Price- Best	Unit type (EA, ML, GM)	Total Unit Volume
00003-0894-70	2021-Q1				EA	
00003-0894-70	2020-Q4				EA	
00003-0894-70	2020-Q3				EA	
00003-0894-70	2020-Q2				EA	
00003-0894-70	2020-Q1				EA	
00003-0894-70	2019-Q4				EA	
00003-0894-70	2019-Q3				EA	
00003-0894-70	2019-Q2				EA	
00003-0894-70	2019-Q1				EA	
00003-0894-70	2018-Q4				EA	
00003-0894-70	2018-Q3				EA	
00003-0894-70	2018-Q2				EA	
00003-3764-74	2023-Q1				EA	
00003-3764-74	2022-Q4				EA	
00003-3764-74	2022-Q3				EA	
00003-3764-74	2022-Q2				EA	
00003-3764-74	2022-Q1				EA	
00003-3764-74	2021-Q4				EA	
00003-3764-74	2021-Q3				EA	
00003-3764-74	2021-Q2				EA	
00003-3764-74	2021-Q1				EA	
00003-3764-74	2020-Q4				EA	

G. Market Data and Revenue and Sales Volume Data

U.S. Commercial Average Net Unit Price

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

National Drug Code (NDC-11)	Quarter	U.S. Commercial Average Unit Net Price	U.S. Commercial Average Net Unit Price - Without Patient Assistance Programs	U.S. Commercial Average Net Unit Price- Best	Unit type (EA, ML, GM)	Total Unit Volume
00003-3764-74	2020-Q3				EA	
00003-3764-74	2020-Q2				EA	
00003-3764-74	2020-Q1				EA	
00003-3764-74	2019-Q4				EA	
00003-3764-74	2019-Q3				EA	
00003-3764-74	2019-Q2				EA	
00003-3764-74	2019-Q1				EA	
00003-3764-74	2018-Q4				EA	
00003-3764-74	2018-Q3				EA	
00003-3764-74	2018-Q2				EA	

Explanations: BMS has filed a lawsuit challenging the Drug Price Negotiation Program, Bristol Myers Squibb Company. v. Becerra et al., No. 3:23-03335 (D.N.J.). As alleged in the complaint BMS filed in that suit (BMS Complaint), BMS does not agree, and its signature to the “Agreement” should not be construed as implying agreement, with the characterizations, express or implied, in such “Agreement” or that any resulting price of the so-called negotiation is “fair.” BMS reserves all of its rights with respect to the Drug Price Negotiation Program, including the legal claims presented in the BMS Complaint.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

The information provided in Section I (Evidence About Alternative Treatments) provides a more appropriate basis than market data and sales volume data for determining the offer and counteroffer because the Evidence About Alternative Treatments better reflects the clinical attributes of Eliquis and evidence of its benefits to patients, the healthcare system, and society. This response contains confidential, proprietary, and trade secret information that is exempt from disclosure under the Inflation Reduction Act (Social Security Act § 1193(c)), Freedom of Information Act Exemption 4 (5 U.S.C. § 552(b)(4)), and the Trade Secrets Act (18 U.S.C. § 1905).

Manufacturer E2 Submission – Bristol Meyers Squibb



Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	APIXABAN
	Respondent Name	[REDACTED]
	Organization Name (if applicable)	BMS
	Respondent Email	[REDACTED]
	Who is completing this form?	
Question 27: Prescribing Information	Prescribing Information	<p>As stated elsewhere and incorporated here by reference, BMS reserves all of its rights with respect to the Drug Price Negotiation Program, including the legal claims presented in its Complaint.</p> <p>27.1 INTRODUCTION</p> <p>Eliquis® is the leading direct oral anticoagulant (DOAC) in the United States (US) Medicare population to reduce risk of stroke and blood clots in patients with nonvalvular atrial fibrillation (NVAF) and treat blood clots in the legs or lungs and help reduce risk of recurrence in patients with venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE). Other oral anticoagulants (OACs) available in the US include warfarin, a vitamin K antagonist (VKA), and [REDACTED]. [REDACTED] Warfarin is not clinically comparable to Eliquis for the reasons described in Q27. We present detailed evidence regarding the clinical and economic differentiation of Eliquis and other DOACs that might be considered therapeutic alternatives in Q28 and Q29.</p> <p>[REDACTED]</p> <p>27.2 ELIQUIS US PRESCRIBING INFORMATION</p> <p>Eliquis (apixaban), an oral factor Xa inhibitor anticoagulant, is approved by the US Food and Drug Administration (FDA) (1) to reduce risk of stroke and SE in NVAF patients; (2) for prophylaxis of DVT, which may lead to PE, following</p>



Question	Sub-Question	Response
		<p>hip or knee replacement surgery; (3) for DVT treatment; (4) for PE treatment; and (5) to reduce risk of recurrence of DVT and PE following initial therapy [2].</p> <p>27.3 THERAPEUTIC ALTERNATIVE</p> <p>In addition to Eliquis, OACs approved by FDA for similar indications include warfarin and other DOACs [REDACTED]. Warfarin was the primary OAC treatment until FDA approval of DOACs. Warfarin is not clinically comparable to Eliquis because: (1) Updated guidelines recommend DOACs as first-line treatment over warfarin for stroke prevention in DOAC-eligible NVAf patients and for DVT/PE treatment and recurrent DVT/PE prevention in DOAC-eligible patients (Q28.2); (2) randomized clinical trials (RCTs) and abundant CER consistently demonstrate that Eliquis has lower risk of stroke/SE and MB versus warfarin in NVAf patients and has lower risk of MB in VTE patients (Q27, Q28, Q29); (3) warfarin requires routine monitoring, has a narrow therapeutic window, has a highly variable dose response, and is associated with food/drug interactions [3].</p> <p>We present detailed clinical and economic evidence demonstrating differentiation of Eliquis from other DOACs in Q28 and Q29. [REDACTED]</p> <p>27.4 STROKE/SE RISK REDUCTION IN NVAf</p> <p>Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with significantly increased risk of stroke and mortality [6]. AF is the primary diagnosis in > 454,000 hospitalizations annually and contributes to 158,000 deaths annually [7]. Stroke occurs 45 times more often in patients with AF. t [8]. NVAf (defined as AF in the absence of moderate-to-severe mitral stenosis or a mechanical heart valve [6]) is the most prevalent type of AF. In 2018, there were 6.4-7.4 million NVAf diagnoses [9].</p> <p>In the absence of contraindications, OAC therapy is a mainstay of stroke/SE risk reduction in NVAf patients at high risk of stroke, defined as a CHA2DS2VASc score ≥ 2. The CHA2DS2-VASc score is a risk stratification tool to estimate stroke risk in AF patients; this score assigns 1 point to each of these risk factors (except as noted): congestive heart</p>



Question	Sub-Question	Response
		<p>failure, hypertension, age (2 points for ≥ 75 years; 1 point for 65-74 years), diabetes, prior stroke or transient ischemic attack or thromboembolism (2 points), vascular disease, and female sex. Bleeding is the most common and serious complication associated with OAC therapy [6,10].</p> <p>Warfarin was the primary OAC treatment until US approval of DOACs. The AHA/ACC/HRS guideline recommends DOACs over warfarin for stroke prevention in DOAC-eligible AF patients [6], and CHEST guideline recommends DOACs over warfarin for VTE treatment [11]. Head-to-head RCTs have demonstrated that each DOAC is noninferior or superior to warfarin in reducing stroke for NVAF patients, with a similar or reduced risk of MB [12-15]. Eliquis is the only DOAC shown in RCTs to be superior to warfarin for reduction of stroke/SE, MB, and all-cause mortality in NVAF patients and is the only DOAC without increased risk of gastrointestinal (GI) bleeding versus warfarin [12-15].</p> <p>ARISTOTLE a phase 3, double-blind RCT compared efficacy and safety of Eliquis 5 mg twice daily versus warfarin in NVAF. Rates of stroke/SE (hazard ratio [HR], 0.79; 95% confidence interval [CI], 0.66-0.95; $P = 0.01$), MB (HR, 0.69; 95% CI, 0.60-0.80; $P < 0.0001$), and all-cause mortality (HR, 0.89; 95% CI, 0.80-0.998; $P = 0.047$) were significantly lower with Eliquis versus warfarin [2,12]. AVERROES a phase 3, double-blind RCT compared the efficacy and safety of Eliquis 5 mg twice daily versus aspirin in NVAF patients who failed or were unsuitable for VKA therapy. Eliquis was superior to aspirin in reducing risk of stroke/SE (HR, 0.45; 95% CI, 0.32-0.62; $P < 0.001$) without significantly increasing the risk of MB (HR, 1.54; 95% CI, 0.96-2.45; $P = 0.07$) or intracranial hemorrhage (ICH) (HR, 0.99; 95% CI, 0.39-2.51) [2,16].</p> <p>27.5 TREATMENT OF VTE AND PREVENTION OF RVTE</p> <p>Eliquis is used for VTE treatment and rVTE prevention. The incidence of VTE increases with age, especially after 50-60 years [17-19]; in individuals with cancer [20]; and in those undergoing surgery [18]. The number of US adults with VTE is projected to rise from 0.95 million in 2006 to 1.82 million by 2050 due to the aging population [17].</p> <p>Current guidelines recommend DOACs over warfarin for VTE treatment and rVTE prevention [11,21,22]. Unlike warfarin, DOACs do not require routine INR monitoring and have fewer drug and food interactions [2-4,23,24]. RCTs have shown that DOACs are noninferior to warfarin in reducing risk of rVTE and VTE-related death and confer a comparable or reduced bleeding risk [25-30]. [REDACTED]</p> <p>The AMPLIFY and AMPLIFY-EXT studies provided evidence for efficacy and safety of Eliquis in VTE treatment and rVTE prevention following 6-12 months of anticoagulant treatment. AMPLIFYa phase 3, double-blind, noninferiority</p>



Question	Sub-Question	Response
		<p>RCT compared efficacy and safety of Eliquis versus Lovenox (enoxaparin) followed by warfarin to prevent rVTE or VTE-related death in patients with acute DVT, PE, or both. Eliquis had comparable efficacy in composite rVTE/VTE-related death (relative risk [RR], 0.84; 95% CI, 0.60-1.18; $P < 0.0001$ for noninferiority) and lower risk of MB (RR, 0.31; 95% CI, 0.17-0.55; $P < 0.0001$) versus Lovenox/warfarin [2,25].</p> <p>AMPLIFY-EXT a phase 3, double-blind RCT compared efficacy and safety of extended Eliquis treatment versus placebo beyond the initial 6-12 months of anticoagulation therapy. Eliquis 2.5 mg had superior efficacy in composite rVTE/all-cause death (RR, 0.33; 95% CI, 0.22-0.48; $P < 0.0001$) and a similar rate of MB ($P =$ not significant) versus placebo [2,31].</p> <p>27.6 VTE PROPHYLAXIS AFTER KNEE/HIP REPLACEMENT SURGERY</p> <p>Eliquis is used for VTE prophylaxis after knee/hip replacement surgery. The CDC estimates that 719,000 total knee replacement surgeries and 332,000 total hip replacement surgeries are performed in the US annually [32]. Hip or knee replacements are strong risk factors for VTE [33]. Without thromboprophylaxis, the rate of nonfatal, symptomatic VTE during 35 days after major orthopedic surgery is estimated at 4.3% (DVT, 2.8%; PE, 1.5%). Prophylactic treatment with OACs is recommended to reduce risk of VTE after total knee or total hip replacement [34].</p> <p>ADVANCE a pair of phase 3, double-blind RCTs compared Eliquis with Lovenox for VTE prophylaxis in patients undergoing total knee or total hip replacement surgeries. Eliquis 2.5 mg twice daily reduced the incidence of composite VTE/all-cause death and had a comparable incidence of composite MB/clinically relevant nonmajor bleeding versus Lovenox 40 mg once daily subcutaneously [2,35-37].</p> <p>Please see US FULL PRESCRIBING INFORMATION, including Boxed WARNINGS, and Medication Guide.</p> <p>REFERENCES</p> <p>1. By the 2023 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2023 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2023 Jul;71(7):2052-81.</p> <p>2. ELIQUIS® (apixaban) [prescribing information]. Princeton, NJ: Bristol Myers Squibb; 2021.</p> <p>[REDACTED]</p> <p>5. Atwater BD et al. Temporal trends in anticoagulation use and clinical outcomes among medicare beneficiaries</p>



Question	Sub-Question	Response
		<p>with non-valvular atrial fibrillation. J Thromb Thrombolysis. 2023 Aug 2.</p> <p>6. January CT et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. Circulation. 2019 Jul 9;140(2):e125-e51.</p> <p>7. Benjamin EJ et al. American Heart Association Council on E, Prevention Statistics C, Stroke Statistics S. Heart disease and stroke statistics-2019 update: a report from the American Heart Association. Circulation. 2019 Mar 5;139(10):e56-e528.</p> <p>8. Tsao CW et al. Heart disease and stroke statistics-2022 update: a report from the American Heart Association. Circulation. 2022 Feb 22;145(8):e153-e639.</p> <p>9. Saeed H et al. National Physician Survey for Nonvalvular Atrial Fibrillation (NVAf) anticoagulation comparing knowledge, attitudes and practice of cardiologist to PCPs. Clin Appl Thromb Hemost. 2020 Jan-Dec;26:1076029620952550.</p> <p>10. Lip GYH et al. Antithrombotic therapy for atrial fibrillation: CHEST guideline and expert panel report. Chest. 2018;154(5):1121-201.</p> <p>11. Stevens SMet al.. Antithrombotic therapy for VTE disease: second update of the CHEST guideline and expert panel report. Chest. 2021 Dec;160(6):e545-e608.</p> <p>12. Granger CBet al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011 Sep 15;365(11):981-92.</p> <p>13. Connolly SJ et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009 Sep 17;361(12):1139-51.</p> <p>14. Giugliano RP et al.. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013 Nov 28;369(22):2093-104.</p> <p>15. Patel MRet al.. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011 Sep 8;365(10):883-91.</p> <p>16. Connolly SJ et al.. Apixaban in patients with atrial fibrillation. N Engl J Med. 2011 Mar 3;364(9):806-17.</p> <p>17. Deitelzweig SB, Johnson BH, Lin J, Schulman KL. Prevalence of clinical venous thromboembolism in the USA: current trends and future projections. Am J Hematol. 2011;86(2):217-20.</p> <p>18. Pannucci CJ, Shanks A, Moote MJ, Bahl V, Cederna PS, Naughton NN, Wakefield TW, Henke PK, Campbell DA, Kheterpal S. Identifying patients at high risk for venous thromboembolism requiring treatment after outpatient surgery. Ann Surg. 2012 Jun;255(6):1093-9.</p> <p>19. Heit JA. Epidemiology of venous thromboembolism. Nat Rev Cardiol. 2015 Aug;12(8):464-74.</p> <p>20. Girardi L, Wang TF, Ageno W, Carrier M. Updates in the incidence, pathogenesis, and management of cancer and venous thromboembolism. Arterioscler Thromb Vasc Biol. 2023 Jun;43(6):824-31.</p> <p>21. Ortel TL, Neumann I, Ageno W, Beyth R, Clark NP, Cuker A, Hutten BA, Jaff MR, Manja V, Schulman S, Thurston C,</p>



Question	Sub-Question	Response
		<p>Vedantham S, Verhamme P, Witt DM, I DF, Izcovich A, Nieuwlaat R, Ross S, H JS, Wiercioch W, Zhang Y, Zhang Y. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. Blood Adv. 2020 Oct 13;4(19):4693-738.</p> <p>22. Referenced with permission from the NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines®) for Cancer-Associated Venous Thromboembolic Disease. V.1.2022. ©2022 National Comprehensive Cancer Network, Inc. All rights reserved. Accessed on February 15, 2023. To view the most recent and complete version of the guideline, go online to NCCN.org.</p> <p>[REDACTED]</p> <p>25. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Masiukiewicz U, Pak R, Thompson J, Raskob GE, Weitz JI. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med. 2013;369(9):799-808.</p> <p>26. Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, Baanstra D, Schnee J, Goldhaber SZ. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med. 2009 Dec 10;361(24):2342-52.</p> <p>27. Schulman S, Kakkar AK, Goldhaber SZ, Schellong S, Eriksson H, Mismetti P, Christiansen AV, Friedman J, Le Maulf F, Peter N, Kearon C. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. Circulation. 2014 Feb 18;129(7):764-72.</p> <p>28. Buller HR, Decousus H, Grosso MA, Mercuri M, Middeldorp S, Prins MH, Raskob GE, Schellong SM, Schwocho L, Segers A, Shi M, Verhamme P, Wells P. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med. 2013 Oct 10;369(15):1406-15.</p> <p>29. Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, Gallus AS, Lensing AW, Misselwitz F, Prins MH, Raskob GE, Segers A, Verhamme P, Wells P, Agnelli G, Bounameaux H, Cohen A, Davidson BL, Piovella F, Schellong S. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med. 2010 Dec 23;363(26):2499-510.</p> <p>30. Buller HR, Prins MH, Lensin AW, Decousus H, Jacobson BF, Minar E, Chlumsky J, Verhamme P, Wells P, Agnelli G, Cohen A, Berkowitz SD, Bounameaux H, Davidson BL, Misselwitz F, Gallus AS, Raskob GE, Schellong S, Segers A. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med. 2012 Apr 05;366(14):1287-97.</p> <p>31. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Porcari A, Raskob GE, Weitz JI. Apixaban for extended treatment of venous thromboembolism. N Engl J Med. 2013;368(8):699-708.</p> <p>32. CDC. Centers for Disease Control and Prevention. National hospital discharge survey: 2010 table, procedures by selected patient characteristics - number by procedure category and age. 2010.</p> <p>33. Anderson FA, Jr., Spencer FA. Risk factors for venous thromboembolism. Circulation. 2003 Jun 17;107(23 Suppl 1):I9-16.</p> <p>34. Falck-Ytter Y, Francis CW, Johanson NA, Curley C, Dahl OE, Schulman S, Ortel TL, Pauker SG, Colwell CW, Jr. Prevention of VTE in orthopedic surgery patients: antithrombotic therapy and prevention of thrombosis, 9th ed:</p>



Question	Sub-Question	Response
		<p>American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e278S-325S.</p> <p>35. Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Portman RJ. Apixaban or enoxaparin for thromboprophylaxis after knee replacement. N Engl J Med. 2009 Aug 6;361(6):594-604.</p> <p>36. Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Hornick P. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. Lancet. 2010 Mar 6;375(9717):807-15.</p> <p>37. Lassen MR, Gallus A, Raskob GE, Pineo G, Chen D, Ramirez LM. Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. N Engl J Med. 2010 Dec 23;363(26):2487-98.</p>
	Evidence Submitted include a cost-effectiveness measure?	N
	What type of Evidence is shown?	
Question 28: Therapeutic Impact and Comparative Effectiveness	Therapeutic Impact and Comparative Effectiveness	<p>As stated elsewhere and incorporated here by reference, BMS reserves all of its rights with respect to the Drug Price Negotiation Program, including the legal claims presented in its Complaint.</p> <p>28.1 INTRODUCTION</p> <p>Consistent with randomized clinical trials (RCTs) and CER that compare Eliquis with other oral anticoagulants (OACs) in patients with nonvalvular atrial fibrillation (NVAF) or venous thromboembolism (VTE), current clinical guidelines support the positive and differential benefit of Eliquis [1-5].</p> <p>28.2 SELECTED GUIDELINE RECOMMENDATIONS ON THE MANAGEMENT OF PATIENTS WITH NVAF OR VTE</p> <div style="background-color: black; width: 100%; height: 150px; margin-top: 10px;"></div>

Question	Sub-Question	Response
		<div data-bbox="632 289 1997 402" style="background-color: black; height: 70px; width: 100%;"></div> <p data-bbox="632 435 1997 540">For the management of VTE in cancer patients, the ASH 2021 and NCCN® 2023 guidelines recommend the use of DOACs over VKAs for initial management in patients with deep vein thrombosis (DVT) and pulmonary embolism (PE) and suggests DOACs over low-molecular-weight heparin or VKA for management of VTE [3,4].</p> <p data-bbox="632 573 1997 646">In 2023, the AGS updated the Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults (i.e., those aged ≥ 65 years). Strong recommendations include:</p> <ul data-bbox="632 678 1997 751" style="list-style-type: none"> • For warfarin: “Avoid starting warfarin as initial therapy for the treatment of NVAf or VTE unless alternative options (i.e., DOACs) are contraindicated or there are substantial barriers to their use” [5]. <div data-bbox="632 784 1986 898" style="background-color: black; height: 70px; width: 100%;"></div> <div data-bbox="632 930 1934 1076" style="background-color: black; height: 90px; width: 100%;"></div> <p data-bbox="632 1109 1997 1287">For NVAf patients with end-stage renal disease or on hemodialysis, the AHA/ACC/HRS 2019 focused update recommends the following (class IIb B-NR): “For patients with AF who have a CHA2DS2-VASc score of 2 or greater in men or 3 or greater in women and who have end-stage chronic kidney disease (CKD; creatinine clearance [CrCl] < 15 mL/min) or are on dialysis, it might be reasonable to prescribe warfarin (INR 2.0 to 3.0) or [Eliquis] for oral anticoagulation.”</p> <div data-bbox="632 1287 1997 1369" style="background-color: black; height: 50px; width: 100%;"></div> <p data-bbox="632 1401 957 1433">28.3 CER STUDY SELECTION</p> <p data-bbox="632 1466 1997 1531">A literature search conducted across multiple databases identified CER studies that compared Eliquis with warfarin, in patients with NVAf or VTE. Figure 1 outlines the study inclusion/exclusion criteria. Only CER</p>



Question	Sub-Question	Response
		<p>studies that were based on analyses of administrative claims data from Medicare fee-for-service (FFS) or Medicare Advantage (MA) plans or administrative claims data pooled from Medicare (FFS or MA plans) and commercial plans in the US were selected. [REDACTED] The cohort sample size for most studies ranges from 10,000-100,000. All studies used methods to adjust for potential confounders, with most using 1:1 propensity score matching.</p> <p>Identified studies were summarized based on the NVAf and VTE indications, respectively. Both clinical and economic outcomes were evaluated. Additionally, evidence about patient experience, such as persistence with treatment, consequences of switching from Eliquis, and patient-centric outcomes, was also presented. Key clinical outcomes for NVAf (stroke/systemic embolism [SE] and major bleeding [MB]) and for VTE (rVTE, MB, and clinically relevant nonmajor bleeding [CRNMB]) were selected to be consistent with pivotal DOAC trials to enable comparison and interpretation between RCT and CER. For economic outcomes, both all-cause costs and costs related to the clinical outcomes, such as stroke/SE-related and MB-related costs for NVAf and rVTE-related and MB-related costs for VTE, were presented.</p> <p>28.4 CER ON STROKE/SE RISK REDUCTION IN NVAf PATIENTS</p> <p>28.4.1 CER ON ELIQUIS VERSUS WARFARIN: STROKE/SE AND MB</p> <p>Consistent with the ARISTOTLE trial, 7 CER studies showed that Eliquis was associated with a lower risk of stroke/SE and MB versus warfarin [REDACTED] [6-12].</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>



Question	Sub-Question	Response
		<div></div> <div></div> <p>28.4.4 CER ON ELIQUIS VERSUS OTHER OACS: COSTS</p> <p>The clinical benefits of Eliquis versus other OACs have translated into economic benefits in NVAf patients. Cost analyses based on data from Medicare FFS or MA plans show that NVAf patients receiving Eliquis have lower stroke-related and bleeding-related costs as well as lower all-cause costs versus patients receiving warfarin, despite higher pharmacy costs [7,17]. The lower all-cause costs associated with Eliquis versus warfarin suggest that the higher pharmacy costs for patients receiving Eliquis are offset by fewer stroke and bleeding events and other potential complications associated with these events [7,17].</p> <div></div> <div></div> <div></div> <p>28.4.6 COST-EFFECTIVENESS ANALYSIS (CEA) OF ELIQUIS VERSUS OTHER OACS</p> <p>In accordance with CMS final guidance for Negotiation Data Elements issued in July 2023, in which CMS reaffirmed that quality-adjusted life years (QALY) will not be used in the Negotiation Program, BMS is not relying on US and international studies that used QALY as a measure in demonstrating the cost-effectiveness of Eliquis for reduction of risk of stroke and SE in patients with NVAf compared to other OACs, although BMS can provide those references upon request.</p> <div></div> <div></div>

Question	Sub-Question	Response
		[REDACTED]
		[REDACTED]
		[REDACTED]
		28.4.8 CER ON ELIQUIS VERSUS OTHER DOACS: PERSISTENCE OF TREATMENT
		Treatment persistence is associated with better clinical outcomes for NVAf patients, including reduced risk of stroke/SE and improved mortality rates [19]. Dhamane et al. [19] conducted a retrospective cohort study of over 1 million NVAf patients using data from Medicare FFS and 4 US commercial plans. [REDACTED]

Question	Sub-Question	Response
		<p>28.4.9 CER ON ELIQUIS VERSUS OTHER OACS: PATIENT-CENTRIC OUTCOMES</p> <p>A CER study using data from Medicare FFS and commercial plans found that the event-free time gain (95% CI) for Eliquis versus warfarin was 101 days (78-124 days) for stroke/SE and 116 days (103-130 days) for MB during the 12-month follow-up period. [REDACTED]</p> <p>28.5 CER ON TREATMENT OF VTE PATIENTS AND PREVENTION OF RVTE</p> <p>28.5.1 CER ON ELIQUIS VERSUS WARFARIN FOR PRIMARY VTE TREATMENT</p> <p>Five CER studies compared Eliquis with warfarin in VTE patients using administrative claims data from Medicare FFS plans alone or along with data from commercial plans [REDACTED]. Like the AMPLIFY trial, these studies have shown that Eliquis is associated with a lower or similar risk of rVTE and a consistently lower risk of MB versus warfarin in Medicare-inclusive VTE patients [22-26].</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>28.5.3 CER ON ELIQUIS VERSUS OACS FOR EXTENDED VTE TREATMENT</p> <p>Park et al. [29] used data from Medicare FFS plans and found that extended treatment with Eliquis versus warfarin was associated with a lower risk of rVTE (0.19 vs 1.45 per 100-person-years; HR, 0.13; 95% CI, 0.030-0.63) and MB (2.07 vs 3.69 per 100-person-years; HR, 0.56; 95% CI, 0.32-0.98). This study also compared extended Eliquis treatment with no extended treatment and found a lower risk of rVTE with Eliquis (0.17 vs 1.72 per 100-person-years; HR, 0.08; 95% CI, 0.01-0.41) and a similar risk of MB (2.14 vs 1.35 per 100-person-years; HR, 1.29; 95% CI, 0.68-2.45).</p> <p>Pawar et al. [30] used data from MA plus private insurers to compare extended treatment with Eliquis versus warfarin [REDACTED]. The study found a lower risk of rVTE (9.8 vs 13.5; HR, 0.69; 95% CI, 0.49-0.99) with Eliquis versus warfarin and a similar risk of rVTE (9.8 vs 11.6; HR, 0.80; 95% CI, 0.53-1.19) and MB (44.4 vs 50.0; HR, 0.86; 95% CI,</p>

Question	Sub-Question	Response
		<p>0.71-1.04) [REDACTED].</p> <p>28.5.4 CER ON ELIQUIS VERSUS WARFARIN ON COSTS IN VTE PATIENTS</p> <p>One CER study compared economic outcomes between Eliquis and warfarin in VTE patients using Medicare FFS data. Eliquis versus warfarin was associated with lower all-cause health costs (\$3,033 vs \$3,267; P < 0.001), all-cause medical costs (\$2,481 vs \$2,861; P < 0.0001), and MB-related medical costs (\$75 vs \$147; P = 0.003), despite higher pharmacy costs (\$552 vs \$407; P < 0.001) [27].</p>
	Hyperlink to Citation - Additional Materials for Question 28	[REDACTED]
	Hyperlink to Table/Charts/Graphs - Additional Materials for Question 28	[REDACTED]
	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>29.1 INTRODUCTION</p> <p>As stated elsewhere and incorporated here by reference, BMS reserves all of its rights with respect to the Drug Price Negotiation Program, including the legal claims presented in its Complaint.</p> <p>Specific populations of Medicare patients such as those with very old age (≥ 80 years), dementia, end-stage renal disease (ESRD), frailty, multi-morbidity, and high risk of bleeding have been evaluated in comparative effectiveness</p>



Question	Sub-Question	Response
		<p>research (CER) that compared Eliquis® with other oral anticoagulants (OACs) for both nonvalvular atrial fibrillation (NVAf) and venous thromboembolism (VTE). Consistent with the findings from the overall population, these studies demonstrated clinical differentiation of Eliquis versus other OACs in various specific populations.</p> <p>29.2 EVIDENCE EXTRACTION</p> <p>A search of published articles in PubMed identified CER studies for NVAf and VTE that compared Eliquis with warfarin, [REDACTED] in specific subpopulations of patients with NVAf or VTE. Only CER studies that analyzed administrative claims data from Medicare fee-for-service (FFS) or MA plans or administrative claims data pooled from Medicare (FFS or MA plans) and commercial plans in the US were selected. [REDACTED]</p> <p>[REDACTED] The cohort sample size for most of the subpopulations ranges from 10,000 to 100,000. Even the smallest cohort sample size is more than 1,000 participants. All studies used methods to adjust for potential confounders, with most using 1:1 propensity-score matching [REDACTED].</p> <p>29.3 CER ON SPECIFIC POPULATIONS OF NVAf PATIENTS</p> <p>29.3.1 CER ON ELIQUIS VERSUS WARFARIN IN HIGH-RISK SUBPOPULATIONS OF NVAf PATIENTS</p> <p>Fourteen CER studies that compared Eliquis with warfarin evaluated high-risk subpopulations of Medicare-inclusive NVAf patients. These subpopulations included patients with dementia, coronary artery disease (CAD)/PAD, the very elderly (≥ 80 years), diabetes, obesity, frailty, polypharmacy, multi-morbidity, high risk of gastrointestinal (GI) bleed, prior bleed, active cancer, chronic kidney disease (CKD), CKD 3-5, and ESRD. Compared with warfarin, Eliquis consistently demonstrated a lower risk of stroke/systemic embolism (SE) and major bleeding (MB) in all the subpopulations except in patients with ESRD, in whom Eliquis demonstrated a similar risk of stroke/SE [REDACTED] [1-14].</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>



Question	Sub-Question	Response
		<div data-bbox="632 321 1990 506" style="background-color: black; height: 114px; width: 100%;"></div> <p data-bbox="632 540 1276 568">29.4 CER ON SPECIFIC POPULATIONS OF VTE PATIENTS</p> <p data-bbox="632 612 1732 639">29.4.1 CER ON ELIQUIS VERSUS WARFARIN IN HIGH-RISK SUBPOPULATIONS OF VTE PATIENTS</p> <p data-bbox="632 683 1969 857">High-risk subpopulations of Medicare-inclusive VTE patients, including those with CKD, receiving dialysis, with obesity and morbid obesity, and with a high risk of bleeding have been evaluated in 5 CER studies that compared Eliquis with warfarin. Eliquis was associated with a lower risk of rVTE and MB versus warfarin in all the high-risk subpopulations except the lower risk of rVTE versus warfarin in ESRD patients approached statistical significance [15-19].</p> <p data-bbox="632 898 1879 925">29.4.2 CER ON ELIQUIS VERSUS WARFARIN IN VTE PATIENTS BY RACE AND SOCIOECONOMIC STATUS (SES)</p> <p data-bbox="632 969 2005 1143">Cohen et al. [20] conducted an analysis using Medicare FFS data that evaluated the risk of rVTE, MB, and clinically relevant nonmajor bleeding (CRNMB) among VTE patients initiating Eliquis or warfarin by demographic characteristics such as race and SES. The study found that the treatment effects of Eliquis versus warfarin on rVTE and MB were not significantly different (P values for interaction > 0.05) among VTE patients by race (Black vs White) or SES.</p> <div data-bbox="632 1177 1577 1219" style="background-color: black; height: 26px; width: 100%;"></div> <div data-bbox="632 1248 2001 1468" style="background-color: black; height: 135px; width: 100%;"></div> <p data-bbox="632 1502 1757 1529">29.4.4 CER ON ELIQUIS VERSUS OTHER ANTICOAGULANTS IN PATIENTS WITH VTE AND CANCER</p>



Question	Sub-Question	Response
		<p>Patients with cancer are a unique subpopulation of VTE patients. Patients with cancer who develop VTE are at greater risk for rVTE and early death [22,23]. [REDACTED]</p> <p>[REDACTED]. Additionally, a CER study based on data from Medicare FFS and commercial plans found that Eliquis was associated with a lower risk of rVTE (HR, 0.66; 95% CI, 0.53-0.83), MB (HR, 0.68; 95% CI, 0.56-0.83), and CRNMB (HR, 0.74; 95% CI, 0.66-0.83) versus LMWH in Medicare-inclusive patients with VTE and cancer [30].</p>
	Hyperlink to Citation - Additional Materials for Question 29	[REDACTED]
	Hyperlink to Table/Charts/Graphs - Additional Materials for Question 29	[REDACTED]
	Evidence Submitted include a cost-effectiveness measure?	N
	What type of Evidence is shown?	
Question 30: Addressing Unmet Medical Needs	Response to Question 30	<p>As stated elsewhere and incorporated here by reference, BMS reserves all of its rights with respect to the Drug Price Negotiation Program, including the legal claims presented in its Complaint.</p> <p>From 2010-2020, the share of US residents aged ≥ 65 years grew by more than a third [1]. This corresponds to an increasing cardiovascular disease burden, making atrial fibrillation (AF) and venous thromboembolism (VTE) among</p>



Question	Sub-Question	Response
		<p>the leading public health concerns in the US [2]. AF is a prevalent condition that is associated with increased risk of stroke and mortality and has caused substantial clinical and economic burdens to patients and to society [3]. VTE is also a common condition and an important cause of disability and death [4].</p> <p>Oral anticoagulant (OAC) therapies are effective treatments that can reduce the risk of stroke in AF patients and treat VTE and prevent recurrent VTE (rVTE) in VTE patients [5,6]. These therapies have helped address the unmet medical need for both patients with AF and VTE; however, the use of anticoagulants has been associated with an elevated risk of bleeding [3,7]. Evidence presented in this document demonstrates that Eliquis® addresses the unmet medical needs of both patients with AF and VTE better than other OACs.</p> <p>In the past, warfarin was the standard of care for both NVAf and VTE; however, warfarin use has been associated with challenges, such as the need for routine international normalized ratio (INR) monitoring (eg, every 1-4 weeks), a narrow therapeutic window and a highly variable dose response, and associated drug and food interactions [8]. Direct OACs [REDACTED] have been approved globally as alternatives to warfarin [8-12]. Unlike warfarin, DOACs do not require INR monitoring and have fewer drug and food interactions [8-12]. DOACs have been demonstrated in randomized clinical trials (RCTs) to be noninferior to warfarin in preventing stroke for AF patients and in reducing the risk of rVTE and VTE-related death for VTE patients, and to confer a comparable or reduced risk of bleeding for both patients with NVAf and VTE [13-22].</p> <p>[REDACTED] Eliquis is the only DOAC that has been shown in RCTs to be associated with a lower risk of stroke/systemic embolism (SE), major bleeding (MB), and mortality versus warfarin in NVAf patients and is the only DOAC without an increased risk of gastrointestinal (GI) bleeding versus warfarin [9,13-16].</p> <p>[REDACTED]</p> <p>[REDACTED]</p>



Question	Sub-Question	Response
		<p>Patients with cancer are at increased risk for VTE compared with the general population; furthermore, patients with cancer who develop VTE are at greater risk for rVTE and early death [6]. The clinical benefits of Eliquis have also been found in patients with cancer and VTE [42]. [REDACTED]</p> <p>Access to OAC therapy is important for both patients with AF and VTE. However, there have been disparities in access to therapy, with DOACs, in both AF and VTE patient populations. A recent study using Medicare fee-for-service (FFS) data found that, among newly diagnosed AF patients and a CHA2DS2-VASc score ≥ 2 who should receive anticoagulant therapy, Black patients were less likely to receive OAC treatment (specifically DOACs) than White patients [49]. Another study showed that VTE patients with a lower household income were less likely to use DOACs compared with those with a higher household income [50]. Eliquis has been shown to have consistent treatment effects in Medicare patients of Black race or lower socioeconomic status in the VTE patient population [50], offering a treatment option to help address some of this disparity.</p> <p>In summary, findings from RCTs and existing CER studies specific to Medicare populations demonstrate that Eliquis offers therapeutic advantages over currently available OAC treatments for both the AF and VTE patient populations. Compared with other OACs, Eliquis has helped to address the unmet medical needs of both patients with AF and VTE to a larger extent than other OACs.</p>
	<p>Hyperlink to Citation - Additional Materials for Question 30</p>	<p>[REDACTED]</p>
	<p>Hyperlink to Table/Charts/Graphs - Additional Materials for Question 30</p>	<p>[REDACTED]</p>



Question	Sub-Question	Response
	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>As stated elsewhere and incorporated here by reference, BMS reserves all of its rights with respect to the Drug Price Negotiation Program, including the legal claims presented in its Complaint.</p> <div></div> <div></div>



Question	Sub-Question	Response
		[Redacted]
		[Redacted]
		[Redacted]
		[Redacted]



Question	Sub-Question	Response
		[Redacted]
		[Redacted]
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Table 1: Summary of Data Collection and Analysis					
Category	Sub-category	Item 1	Item 2	Item 3	Item 4
Group A	Item 1	10	20	30	40
	Item 2	15	25	35	45
	Item 3	20	30	40	50
	Item 4	25	35	45	55
	Item 5	30	40	50	60
Group B	Item 1	12	22	32	42
	Item 2	18	28	38	48
	Item 3	22	32	42	52
	Item 4	28	38	48	58
	Item 5	32	42	52	62
Group C	Item 1	14	24	34	44
	Item 2	20	30	40	50
	Item 3	24	34	44	54
	Item 4	30	40	50	60
	Item 5	34	44	54	64
Group D	Item 1	16	26	36	46
	Item 2	22	32	42	52
	Item 3	26	36	46	56
	Item 4	32	42	52	62
	Item 5	36	46	56	66
Group E	Item 1	18	28	38	48
	Item 2	24	34	44	54
	Item 3	28	38	48	58
	Item 4	34	44	54	64
	Item 5	38	48	58	68
Group F	Item 1	20	30	40	50
	Item 2	26	36	46	56
	Item 3	30	40	50	60
	Item 4	36	46	56	66
	Item 5	40	50	60	70
Group G	Item 1	22	32	42	52
	Item 2	28	38	48	58
	Item 3	32	42	52	62
	Item 4	38	48	58	68
	Item 5	42	52	62	72
Group H	Item 1	24	34	44	54
	Item 2	30	40	50	60
	Item 3	34	44	54	64
	Item 4	40	50	60	70
	Item 5	44	54	64	74
Group I	Item 1	26	36	46	56
	Item 2	32	42	52	62
	Item 3	36	46	56	66
	Item 4	42	52	62	72
	Item 5	46	56	66	76
Group J	Item 1	28	38	48	58
	Item 2	34	44	54	64
	Item 3	38	48	58	68
	Item 4	44	54	64	74
	Item 5	48	58	68	78
Group K	Item 1	30	40	50	60
	Item 2	36	46	56	66
	Item 3	40	50	60	70
	Item 4	46	56	66	76
	Item 5	50	60	70	80
Group L	Item 1	32	42	52	62
	Item 2	38	48	58	68
	Item 3	42	52	62	72
	Item 4	48	58	68	78
	Item 5	52	62	72	82
Group M	Item 1	34	44	54	64
	Item 2	40	50	60	70
	Item 3	44	54	64	74
	Item 4	50	60	70	80
	Item 5	54	64	74	84
Group N	Item 1	36	46	56	66
	Item 2	42	52	62	72
	Item 3	46	56	66	76
	Item 4	52	62	72	82
	Item 5	56	66	76	86
Group O	Item 1	38	48	58	68
	Item 2	44	54	64	74
	Item 3	48	58	68	78
	Item 4	54	64	74	84
	Item 5	58	68	78	88
Group P	Item 1	40	50	60	70
	Item 2	46	56	66	76
	Item 3	50	60	70	80
	Item 4	56	66	76	86
	Item 5	60	70	80	90

The image is a complex black and white graphic design, possibly a book cover or a page from a magazine. It features a central vertical column of text, flanked by horizontal bars and blocks of text, creating a symmetrical, abstract layout. The text is in a sans-serif font, and the overall composition is highly structured and balanced. The central column contains the most prominent text, while the side elements provide a sense of depth and visual interest. The use of black and white creates a high-contrast, graphic effect. The layout is divided into several horizontal sections by thin lines, and the text is arranged in a way that suggests a narrative or a series of related concepts. The overall impression is one of modernity and artistic sophistication.

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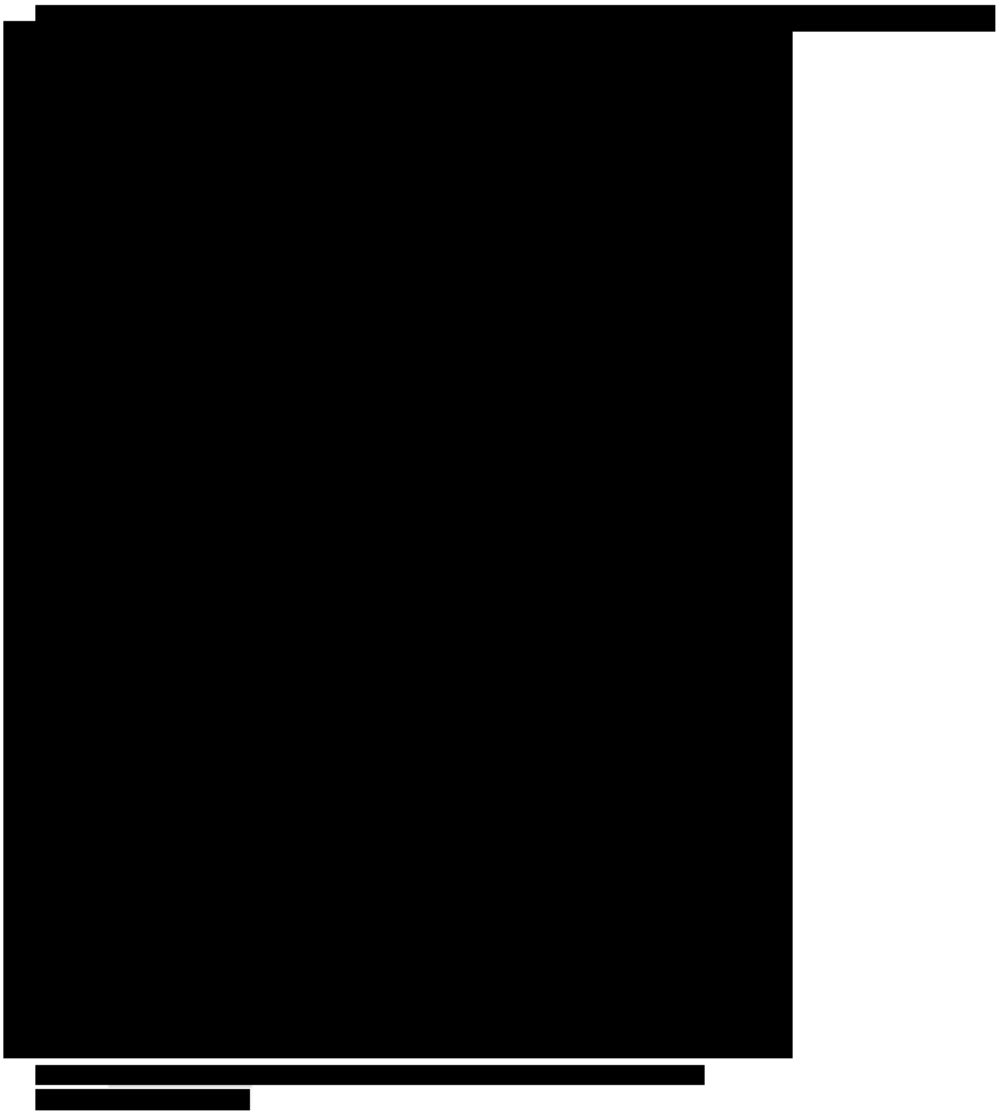
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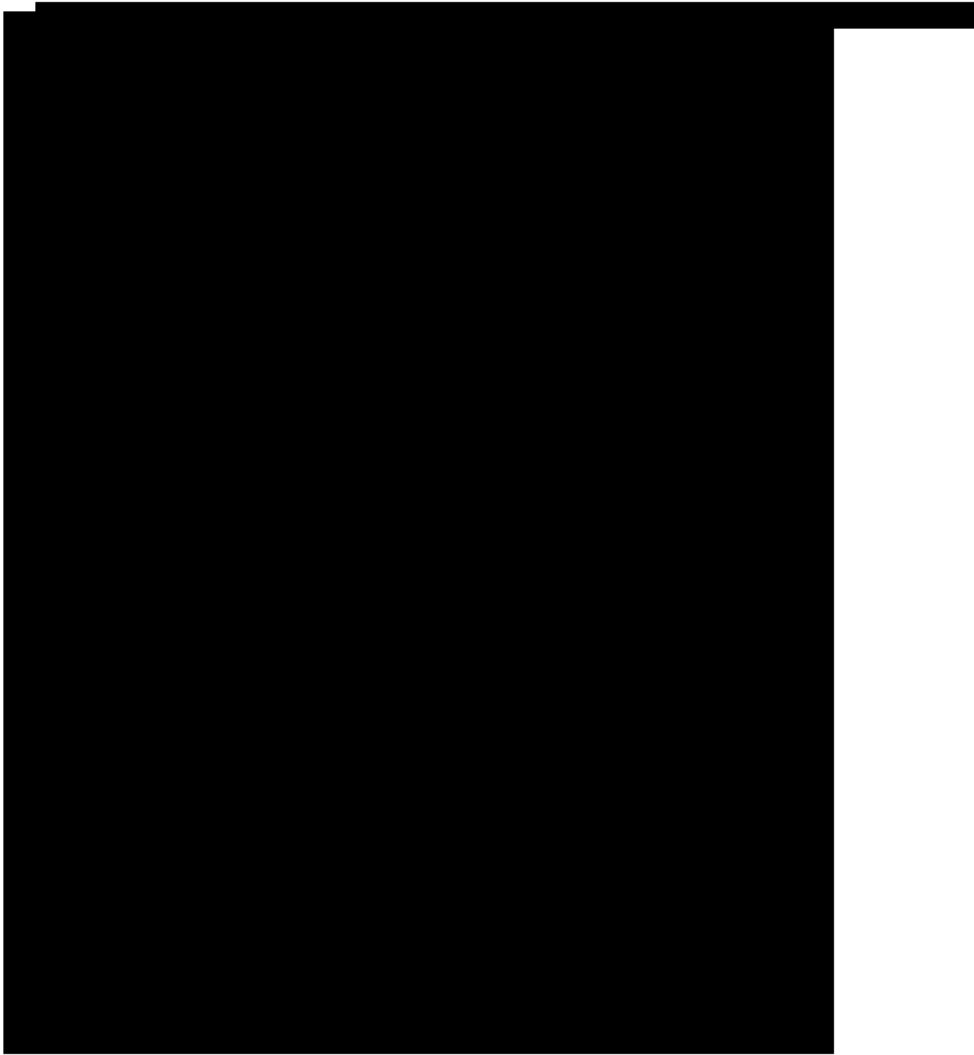
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Public E2 Submission

IPAY: 2026



Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	APIXABAN
	Q26 - Respondent Name	
	Q26 - Organization Name (if applicable)	AARP
	Respondent Email	
	Who is completing this form?	PAT
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	
	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?	

Public E2 Submission

IPAY: 2026



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 Eliquis to treat the condition. [REDACTED] says he fills his prescription through his local Walmart pharmacy, and he must “stretch it” to the last week of the month because he has “other bills he has to take care of.” [REDACTED] lives on fixed Social Security retirement income, must go to Dollar General to be able to afford his food, and says that “to be able to afford [food] and stay healthy is a challenge.” [REDACTED] says he does not understand why Eliquis costs so much when it has been on the market for so long. He feels that there should be cheaper options and that Medicare should be able to negotiate. “Put pressure on the manufacturers!” ..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</p>

Public E2 Submission

IPAY: 2026



Question	Sub-Question
Question 32: Executive Summary	Response to Question 32

Response
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 LeaMond.Executive Vice President and Chief Advocacy & Engagement Officer



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. [REDACTED], a Medicare enrollee from [REDACTED], is living with a health condition and takes Eliquis to treat the condition. [REDACTED] says he fills his prescription through his local Walmart pharmacy, and he must "stretch it" to the last week of the month because he has "other bills he has to take care of." [REDACTED] lives on fixed Social Security retirement income, must go to Dollar General to be able to afford his food, and says that "to be able to afford [food] and stay healthy is a challenge." [REDACTED] says he does not understand why Eliquis costs so much when it has been on

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/>.

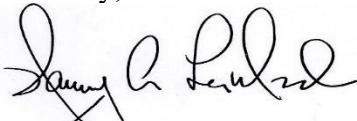
the market for so long. He feels that there should be cheaper options and that Medicare should be able to negotiate. “Put pressure on the manufacturers!”

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	APIXABAN
	Q26 - Respondent Name	
	Q26 - Organization Name (if applicable)	Aimed Alliance
	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	
	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 Aimerd Alliance believes this information is crucial for appropriately determining the negotiated prices, we are concerned that relying on 20 randomly selected speakers will not provide CMS with a comprehensive perspective on these medications and their benefits to patients, providers, and caregivers. We are also concerned that this random selection process could unintentionally exclude speakers who shed light on health equity, minority health, and other access issues.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 Vinenzco Lenti, et al., *Stigmatization and resilience in inflammatory bowel disease patients at one-year follow up*, <https://www.frontiersin.org/articles/10.3389/fgstr.2022.1063325/full>

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Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	APIXABAN
	Q26 - Respondent Name	
	Q26 - Organization Name (if applicable)	Anticoagulation Forum
	Respondent Email	
	Who is completing this form?	HCW
Question 27: Prescribing Information	Prescribing Information	No response
	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	No response
	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	No response

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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	No response
	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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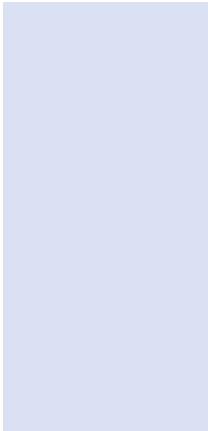
Question	Sub-Question	Response
Question 31: Patient and Caregiver Experience	Response to Question 31	
Question 32: Executive Summary	Response to Question 32	<p>Thank you for offering the opportunity for clinicians and patients to comment on the Drug Price Negotiation Program. ..My name is [REDACTED], MD, MSc and I am an Associate Professor of Internal Medicine at the University of [REDACTED] where I specialize in cardiovascular and vascular medicine. My clinical and research interests focus on delivery of high-quality anticoagulant and antithrombotic therapy to patients with atrial fibrillation, venous thromboembolism, and other cardiovascular conditions. I currently serve as the co-director of the Michigan Anticoagulation Quality Improvement Initiative (MAQI2) and lead several an AHRQ- and NIH-funded studies aiming to improve anticoagulation care and the care of patients with venous thromboembolism. I also serve in leadership positions with the American Heart Association, American College of Cardiology, Society for Vascular Medicine, International Society on Thrombosis and Haemostasis, and the Anticoagulation Forum (AC Forum)...The AC Forum includes more than 13,000 physicians, nurses, and pharmacists representing over 3,000 anticoagulation services (clinics). Our members directly support over 1 million patients annually. Founded 30 years ago, the Anticoagulation Forum is the largest organization of its kind helping practitioners improve patient care by providing current and relevant information on best practices. ..My field of medicine was revolutionized with the advent of the direct oral anticoagulant (DOAC) medications, including apixaban, dabigatran, edoxaban, and rivaroxaban. Clinical studies and real-world evidence have consistently demonstrated their benefits to patients with atrial fibrillation as well as for patients at risk of deep vein thrombosis and pulmonary embolism. ..Multiple studies have demonstrated the superiority of apixaban over warfarin for stroke prevention in atrial fibrillation, the most common indication for chronic anticoagulation. Compared to warfarin, the use of apixaban was shown to lower the risk of stroke or systemic embolization by 21%, major bleeding by over 30%, and death from any cause by 11% in patients with AF. Importantly, the drug also appeared to be very well tolerated, with discontinuation rates lower than warfarin. It is estimated that for every 1000 patients treated with chronic apixaban instead of warfarin, 6 fewer patients would experience stroke, 15 fewer would have major bleeding events, and 8 deaths would be avoided. ..One major benefit of apixaban (and the other DOACs) over warfarin is the predictable dosing, which nearly eliminates the need for frequent blood tests. In fact, I find that having a predictable anticoagulant medication that does not require 1-4 blood draws a month is a leading reason why patients often prefer apixaban over warfarin...It is of the utmost importance that patients who need DOACs can access them at an affordable price. That is why I and many of my colleagues are thankful that the Inflation Reduction Act limited out-of-pocket spending for seniors and smoothed deductible payments over the course of the plan year. However, our community of anticoagulation specialists have seen the consequences of limiting access to anticoagulant options. Too often, patients abandon therapy, which leads to potentially catastrophic cardiovascular events. It</p>

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Question Sub-Question



Response

is critically important, therefore, that through this negotiation process, the Centers for Medicare and Medicaid Services (CMS) ensure that patients can continue to stay on the therapy their doctor prescribes. Re-authorization, step therapy or non-medical switching protocols (often required by pharmacy benefits managers) can discourage adherence, which can be very dangerous for anticoagulant patients. For this policy to patient-centric, cost savings must be passed to patients, and utilization management cannot be used to limit access. ..Lastly, it is important to emphasize that increased access to medications will inevitably be tied to increased prescribing. At present, more than 5 million people in the United States are prescribed an anticoagulant, a number that is anticipated to more than double by 2050 due to secular trends in the population. Concerningly, anticoagulants are the leading cause of emergency department visits and hospital readmissions due to anticoagulant-associated bleeding or thrombotic events. Hence, it is imperative that increased access and prescribing be closely coupled with improved anticoagulant care delivery models, such as anticoagulation stewardship, that have been shown to improve patient safety and outcomes. ..Thank you.

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

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

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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>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.</p>
	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	

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Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	APIXABAN
	Q26 - Respondent Name	
	Q26 - Organization Name (if applicable)	
	Respondent Email	
	Who is completing this form?	HCW
Question 27: Prescribing Information	Prescribing Information	No response
	Evidence Submitted include a cost-effectiveness measure?	N
	What type of Evidence is shown?	
Question 28: Therapeutic Impact and Comparative Effectiveness	Therapeutic Impact and Comparative Effectiveness	No response
	Hyperlink to Table/Charts/Graphs - Additional Materials for Question 28	
	Evidence Submitted include a cost-effectiveness measure?	N
	What type of Evidence is shown?	
	Response to Question 29	No response

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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?	N
	What type of Evidence is shown?	
Question 30: Addressing Unmet Medical Needs	Response to Question 30	No response
	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?	

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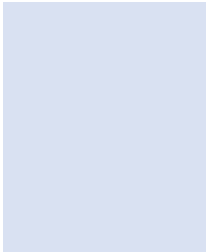
Question	Sub-Question	Response
Question 31: Patient and Caregiver Experience	Response to Question 31	<p>Thank you for the opportunity to provide comments on apixaban for the Medicare Drug Price Negotiation Program for initial price applicability in year 2026. .I am a cardiologist by training, a researcher and [REDACTED] professor [REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED] I have devoted my life to cardiology and the transformative power of preventive medicine. .I am also a patient who owes his life to apixaban. I had life threatening bleeds on warfarin and after many years of enoxaparin injections, apixaban quite literally saved my life. .As you know, apixaban is a factor Xa inhibitor anticoagulant indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. It is also indicated as the treatment of DVT and PE to reduce the risk of recurrence. This latter indication is why I am taking apixaban. Factor Xa induces clotting, and apixaban works by blocking this factor to prevent clotting. .There is no question that apixaban provides immense value for not only patients, but also the healthcare system. Multiple studies have shown that apixaban is a much safer and more effective option than warfarin. A 2019 study demonstrated that, compared to warfarin, a standard-dose DOAC was associated with a 20-29% risk reduction in for thromboembolic stroke, a 35-62% reduction in intracranial hemorrhage, and a 19-34% reduction in mortality.¹ It is true that DOAC spending is increasing, but that is simply a reflection of how much more safe and effective it is than warfarin. Additionally, DOAC use is likely associated with lower downstream medical expenditures compared with warfarin, stemming from decreased risk of major bleeding and stroke and reduced drug monitoring.²The Medicare Drug Price Negotiation Program's stated aim is to lower the price of drugs for Medicare beneficiaries. I am deeply concerned, however, that patients will not actually realize lower prices at the pharmacy counter, as there has been no stated guarantee that cost savings from negotiation will be passed to patients. I am also deeply concerned that without checks, balances, and assurances from pharmacy benefit managers administering formularies, patients will face higher utilization management barriers such as prior authorization, nonmedical switching, and step therapy protocols for negotiated drugs like apixaban. Such practices will likely cause great harm to patients.³ CMS needs to ensure that negotiation accurately reflects the immense value medications like apixaban offer to the Medicare program and to patients themselves; CMS must also ensure that through implementation of the program, access to needed therapy is not limited...¹. Graham DJ, Baro E, Zhang R, Liao J, Wernecke M, Reichman ME, Hu M, Illoh O, Wei Y, Goulding MR, Chillarige Y, Southworth MR, MaCurdy TE, Kelman JA. Comparative Stroke, Bleeding, and Mortality Risks in Older Medicare Patients Treated with Oral Anticoagulants for Nonvalvular Atrial Fibrillation. Am J Med. 2019 May;132(5):596-604.e11. doi:</p>
Question 32: Executive Summary	Response to Question 32	

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Question Sub-Question



Response
10.1016/j.amjmed.2018.12.023. Epub 2019 Jan 9. PMID: 30639551..2. Duvalyan, A., Pandey, A., Vaduganathan, M., Essien, U. R., Halm, E. A., Fonarow, G. C., & Sumarsono, A. (2021). Trends in anticoagulation prescription spending among Medicare Part D and Medicaid beneficiaries between 2014 and 2019. Journal of the American Heart Association, 10(24). <https://doi.org/10.1161/jaha.121.022644>.3. The Impact of Non-Medical Switching on Patients Taking a Blood Thinner. (2022, August). American Society for Preventive Cardiology. <https://www.aspconline.org/wp-content/uploads/2022/08/ASPC-NMSBloodThinner-SurveyReport-August2022.pdf>

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Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	APIXABAN
	Q26 - Respondent Name	
	Q26 - Organization Name (if applicable)	
	Respondent Email	
	Who is completing this form?	PAT
Question 27: Prescribing Information	Prescribing Information	I was not prescribed an alternative. This drug is approved as a blood thinner for reduced chances of stroke due to AFIB
	Evidence Submitted include a cost-effectiveness measure?	D
	What type of Evidence is shown?	
Question 28: Therapeutic Impact and Comparative Effectiveness	Therapeutic Impact and Comparative Effectiveness	I have no knowledge of this.
	Hyperlink to Table/Charts/Graphs - Additional Materials for Question 28	
	Evidence Submitted include a cost-effectiveness measure?	D
	What type of Evidence is shown?	
	Response to Question 29	Unknown by me since I am a patient

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

I have been taking the drug for 2 years. I do not seem to have any adverse side effects and have not used any alternatives. My only concern is the expense and how I can tell if it is doing what it is supposed to do in my body. I am 76 yeas old and still working. If I stop working I will not be able to afford the drug. I have been told that the alternatives to the drug are not ideal and would require blood tests often and would have more side effects. The drug is sometimes not available for a few days after I order it at the Pharmacy. The price of the drug has increased by about 55 dollars in the last couple of months. I phoned by insurance company and the pharmacy, neither has raised the price. I called the manufacturer and was told that the price did go up. It went up in the middle of my contract with my supplemental insurance company.

Question 32:
Executive
Summary

Response to Question 32

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Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	APIXABAN
	Q26 - Respondent Name	
	Q26 - Organization Name (if applicable)	
	Respondent Email	
	Who is completing this form?	PAT
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	
	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	<p>I am a patient who has been taking anticoagulants for 20 years to prevent life-threatening blood clots. I am writing to ask you to please include the patient perspective as you implement the IRA's drug price negotiation program to ensure there are no unintended consequences which may result in reduced treatment access for patients. I am particularly concerned about the possible emergence of stricter utilization management and reduced anticoagulant drug choice in future formularies. ..When I was first diagnosed with venous thromboembolism 20 years ago, I had no drug choice. Generic warfarin was the only oral anticoagulant available at the time. But it is a finicky medication that poses multiple challenges to achieving therapeutic stability – it is very easy to become either over-anticoagulated (increasing the risk of adverse bleeding) or under-anticoagulated (increasing the risk of clot). It necessitates close clinical monitoring consisting of frequent office visits, blood draws and dosage changes – which for me occurred every 2-4 weeks for nearly a decade. To remain in the therapeutic zone, I took a different dose on different days of the week and, as a result, dosing mistakes were not unusual. Because warfarin has many dietary and drug interactions, I had to be constantly hypervigilant about what I ate and took over the counter. When I required operative procedures, there was a high burden coming off warfarin and having to bridge with a costly, injectable low-molecular-weight heparin. ..The scientific development of innovative, new direct oral anticoagulants – Eliquis (apixaban), Xarelto (rivaroxaban), Pradaxa (dabigatran) – was truly a godsend. It allowed me to finally be able to take a more convenient, single-dose anticoagulant that had no dietary restrictions, fewer medication interactions, offered far easier perioperative management and required only an annual office visit for management. In terms of my quality-of-life, there is simply no comparison between the newest direct oral anticoagulant drugs and older warfarin. They liberated me from cumbersome drug management while also lowering my risk of adverse bleeding which is potentially fatal. ..Yet these newest anticoagulants (which do not yet have generic alternatives on the US market) are expensive, accounting for the #1 and #3 drug expenditures for Medicare. Even with insured drug coverage, far too many patients are unable to access these life-changing and life-saving anticoagulants due to either their high cost-share or utilization management restrictions. For that reason, I am truly pleased CMS has included both Eliquis (apixaban) and Xarelto (rivaroxaban) in its first round of price negotiations. Reducing the price of these critical medications, in theory, should improve affordable access for cardiovascular patients. ..However, I am concerned there may be unintended consequences when CMS negotiates prices on these drugs---foremost, that pharmacy benefit managers (PBMs) will in response, implement stricter utilization management policies for anticoagulants and narrow formulary drug choice, thus reducing patient access. I have experienced firsthand and witnessed in many other patients the impact of formulary restrictions and utilization management for anticoagulants, and I cannot state strongly enough the negative impact it has not only on patient quality-of-life, but also directly on health outcomes. ..Easy, affordable access to effective anticoagulation is critical for patients at high-risk of stroke, deep vein thrombosis and pulmonary embolism. These drugs require careful, personalized selection and management. Anticoagulation comes with risk – namely an increased risk of serious, potentially fatal bleeding. Anticoagulants are the #1 drug class for adverse events, resulting in more emergency room visits annually than</p>

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Question	Sub-Question
Question 32: Executive Summary	Response to Question 32

Response
any other drug class, with nearly half of those events being serious enough to warrant a hospital admission. Having a range of affordable, accessible anticoagulant formulary choices means care can be better tailored to the individual patient. Any policy which leads to more limited anticoagulant choice or impedes drug access potentially risks increasing adverse events, which in turn leads to increased medical costs in addition to the human impact. . .Please be vigilant during Medicare's drug price negotiation program implementation of the need of anticoagulated cardiovascular patients to easily and affordably access the treatment chosen through shared-decision making with our doctors who know our unique medical history best. ..Thank you for your time and consideration.

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Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	APIXABAN
	Q26 - Respondent Name	
	Q26 - Organization Name (if applicable)	n/a
	Respondent Email	
	Who is completing this form?	PAT
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	
	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?	



Question	Sub-Question	Response
Question 31: Patient and Caregiver Experience	Response to Question 31	I started taking Eliquis (Apixaban) on 2/15/2022...I think it's reasonable to assume that many who use Eliquis are senior citizens, mostly with less income than when working. In addition, it seems reasonable to surmise that many have more than one medication. Both are true in my case. In and of itself, the cost of Eliquis poses a financial burden...To avoid the financial strain, I was offered warfarin. My Father was put on warfarin after retiring. The frequent medical check-ups were difficult, the side-effects not insignificant, and, most importantly, he nonetheless suffered a debilitating stroke, leaving him paralyzed and without the ability to speak....According to my cardiologist Eliquis is without question the best medication available for my heart condition. I have had no side-effects since taking Eliquis, the drug is easy to monitor, and to date, I have escaped my Father's fate...I encourage you in the strongest possible terms to make Eliquis far more financially accessible to all patients who can benefit medically from it. I thank you for all of your efforts...Thank you for your time and attention, [REDACTED]
Question 32: Executive Summary	Response to Question 32	

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Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	APIXABAN
	Q26 - Respondent Name	
	Q26 - Organization Name (if applicable)	StopAfib.org
	Respondent Email	
	Who is completing this form?	PAT
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	
	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	<p>Thank you for the opportunity to share my experience as an afib patient on oral anticoagulants and that of other afib patients on apixaban. ..Warfarin was our only option before the DOACs (apixaban, rivaroxaban, edoxaban, and dabigatran). But, I was never stable on it. My International Normalized Ratio (INR) would swing wildly between too low (risk of a clot/stroke) and too high (risk of a bleed); I often required multiple blood draws per week to adjust my dose, which took many hours away from work and family. ..In 2005, research showed that one-fourth of those on warfarin were unstable for genetic reasons. I finally understood why I had been through such challenges when it seemed to work fine for others. In talking with afib patients, I found that these challenges with being stable on warfarin appeared to be much more common in women than men. ..Additionally, with warfarin, you must avoid or consistently consume foods containing Vitamin K (i.e., green vegetables). You spend countless hours managing your diet. Warfarin has numerous drug interactions, too. And side effects such as hair loss (falling out in chunks) were common with warfarin...The DOACs were lifesavers – few food and drug interactions and no testing – so we regained our lives and freedom. ..However, pharmacy benefits managers (PBMs) brought back our nightmares. In 2022, one of the largest PBMs dropped three DOACs from their formulary. Hence, patients either paid 100%, applied for Prior Authorizations, or changed meds, returning them to warfarin nightmares. ..As a result of these price negotiations, Prior Authorizations are likely to become even more pervasive and pernicious as payers seek to recapture margins eroded by subsidizing a more significant portion of drug costs. ..My experience with Prior Authorizations is an example of how this hurts patients. As a heart disease patient, I have been on a statin drug for two decades. I tried the generic when my statin went off-patent, and the brand was removed from the formulary. Within two days, my right (dominant) hand was paralyzed; within days of stopping it, I regained the use of my hand. My doctor then requested a Prior Authorization for me to continue on the brand I had been stable on for years. That was approved for several years but has been denied in the past two years. Since then, I have wasted 40-60 hours per year on Prior Authorizations. Most patients cannot spend that time dealing with this (and the stress of doing so is aging me). Last year, my Prior Authorization was denied multiple times, and we went all the way to an Administrative Law Judge Hearing, where the judge found in my favor. Even after that, the insurer has rejected it numerous times this year. ..I am now out of this lifesaving medication. I must wait until next year to try again for Prior Authorization (or take the generic that paralyzed my hand). These games are killing people. I do not want to be one of them, but I cannot afford to pay 100% of the cost of the brand statin I had been stable on for two decades. ..We patients are asking CMS to engage with us throughout this negotiation process and protect us from abusive payers and PBMs. ..While Part D plans must cover drugs selected for negotiation, we fear they will find a way (Tier 4 or non-medical switching) to either make patients pay most of the cost or reduce our access to them and our other medications. They are already working on such strategies; many patients have just received notice that 2024 Part D premiums are doubling. ..These negotiations will pressure PBMs to non-medically switch us (playing doctor once again), which is deadly for us. With many afib patients being on beta blockers that cause confusion, being non-medically switched among different anticoagulant dosing regimens can result in overdosing or underdosing, thus leading to deadly bleeds</p>

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Question

Sub-Question

Response

and strokes. ..Please protect us from these catastrophic consequences caused by payers/PBMs decreasing our access to lifesaving meds...Thank you.

Question 32:
Executive
Summary

Response to Question 32

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Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	APIXABAN
	Q26 - Respondent Name	
	Q26 - Organization Name (if applicable)	Institute for Clinical and Economic Review
	Respondent Email Who is completing this form?	NAR
Question 27: Prescribing Information	Prescribing Information	<p>1.1. Introduction..As a result of the Inflation Reduction Act (IRA), the Centers for Medicare & Medicaid Services (CMS) will soon begin negotiating prices for certain high-expenditure drugs. This submission examines the direct-acting oral anticoagulants (DOACs) apixaban (Eliquis®, Bristol Myers Squibb / Pfizer) and rivaroxaban (Xarelto®, Janssen Pharmaceuticals, Inc.), two of the 10 drugs that CMS has selected for negotiation in the first round. The information in the submission is tailored to reflect legislative specifications in the IRA and subsequent CMS guidance. It is not comprehensive but does include sections on multiple elements related to drug value, providing different options for translating evidence into initial offer prices and for assessing counteroffers from drug makers. We focused on the use of these two drugs for non-valvular atrial fibrillation (NVAf) since that represents the vast majority of use for drugs in this class. As clinical and cost comparators, we selected warfarin, an older generic medication that was the standard therapy for atrial fibrillation prior to the DOACs, and dabigatran, which is the first DOAC available as a generic medication as of 2022...These DOACs have several FDA indications. However, data suggest that the vast majority of DOAC use is for the prevention of stroke and systemic embolism in people with non-valvular atrial fibrillation (NVAf) [IPD Analytics, 2021]. CMS will be able to use its own data to confirm the relative percentage of use of apixaban and rivaroxaban for different indications...Specialty society guidelines (e.g., the American College of Chest Physicians [CHEST] guidelines) suggest that the use of these medications for NVAf be guided by the risk for stroke using one of two risk prediction tools: the CHADS₂ score (one point for each of congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and one points for stroke) or an updated version: the CHA₂DS₂-VASc score which adds three additional risk factors (vascular disease [coronary artery disease, peripheral artery disease, aortic atherosclerosis], age 65-74 years, and female sex). The benefits of stroke prevention with these medications are balanced by the risk for bleeding, which is most commonly estimated using the HAS-BLED score (one point for each risk factor: hypertension, abnormal renal and liver function, stroke, bleeding, labile INR [international normalized ratio], elderly, drugs or alcohol). For all three risk prediction tools, higher scores correspond to higher risk</p>

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Question	Sub-Question
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Response

for the predicted outcome...1.2. Prescribing Information..The prescribing information for the four drugs is summarized below.

- Apixaban (Eliquis®, Bristol Myers Squibb / Pfizer)
- Mechanism of Action: Factor Xa inhibitor
- Dose: 2.5 or 5 mg by mouth twice daily. For NVAf, 5 mg orally twice daily. In patients with at least two of the following characteristics: age greater than or equal to 80 years, body weight less than or equal to 60 kg, or serum creatinine greater than or equal to 1.5 mg/dL, the recommended dose is 2.5 mg orally twice daily.
- Indication:
- Reduce the risk of stroke and systemic embolism in patients with NVAf
- Prophylaxis of deep vein thrombosis (DVT) in patients who have undergone knee or hip replacement
- Treatment of DVT and pulmonary embolism (PE) and to reduce the risk of recurrent DVT and PE
- Rivaroxaban (Xarelto®, Janssen Pharmaceuticals Inc.)
- Mechanism of Action: Factor Xa inhibitor
- Dose: 15 or 20 mg by mouth once daily with food
- Indications:
- To reduce risk of stroke and systemic embolism in nonvalvular atrial fibrillation
- For treatment of DVT
- For treatment of PE
- For reduction in the risk of recurrence of DVT or PE
- For the prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery
- For prophylaxis of venous thromboembolism (VTE) in acutely ill medical patients
- To reduce the risk of major cardiovascular events in patients with CAD
- To reduce the risk of major thrombotic vascular events in patients with PAD, including patients after recent lower extremity revascularization due to symptomatic PAD
- For treatment of VTE and reduction in the risk of recurrent VTE in pediatric patients from birth to less than 18 years
- For thromboprophylaxis in pediatric patients two years and older with congenital heart disease after the Fontan procedure
- Warfarin

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Question	Sub-Question	Response
		<ul style="list-style-type: none"> • Mechanism of Action: Vitamin K antagonist • Dose: By mouth once daily with individualized dosing regimen based on INR results • Indications: • Prophylaxis and treatment of venous thrombosis and its extension, pulmonary embolism • Prophylaxis and treatment of thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement • Reduction in the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction
		<ul style="list-style-type: none"> • Dabigatran • Mechanism of Action: Direct thrombin inhibitor • Dose: 75 or 150 mg by mouth once daily. For NVAf: 150 mg orally, twice daily for patients with CrCl >30 mL/min or 75mg orally, twice daily for patients with CrCl 15-30 mL/min • Generics first approved on March 11, 2020 (Alkem Labs LTD) and May 6, 2020 (Hetero Labs LTD), and launched in 2022 • Indications: • To reduce the risk of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation • For the treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE) in adult patients who have been treated with a parenteral anticoagulant for 5-10 days • To reduce the risk of recurrence of DVT and PE in adult patients who have been previously treated • For the prophylaxis of DVT and PE in adult patients who have undergone hip replacement surgery • For the treatment of venous thromboembolic events (VTE) in pediatric patients 8 to less than 18 years of age who have been treated with a parenteral anticoagulant for at least 5 days • To reduce the risk of recurrence of VTE in pediatric patients 8 to less than 18 years of age who have been previously treated
	Evidence Submitted include a cost-effectiveness measure?	N
	What type of Evidence is shown?	
Question 28: Therapeutic Impact and	Therapeutic Impact and Comparative Effectiveness	<p>3.1. Interventions and Therapeutic Alternatives..To estimate the comparative therapeutic impact of apixaban and rivaroxaban in NVAf, we compared each drug to both warfarin and dabigatran...3.2. Comparative Clinical Effectiveness..3.2.1. Methods Overview..We focused on patient-important outcomes and adverse events, including stroke/systemic embolism (SE), myocardial infarction (MI), bleeding rates, and all-cause mortality.</p>

Question Sub-Question

Comparative
Effectiveness

Response

Outcome definitions are reported in Supplement Table A1.(1) For comparisons with warfarin, we focused on head-to-head randomized controlled trials (RCTs) with the interventions of interest. For comparisons with dabigatran, we conducted Bayesian network meta-analyses (NMAs) of RCTs. We also reviewed evidence from high-quality observational studies on long-term outcomes and harms. The full scope and procedures for the systematic literature review are detailed in the Supplement.(1)..Evidence Base..We examined direct evidence comparing apixaban and rivaroxaban with warfarin from the ARISTOTLE and ROCKET AF trials, respectively. We used the RE-LY trial of dabigatran versus warfarin to conduct indirect analyses comparing the DOACs. These trials are described in the Supplement and in Table 3.1...3.2.2. Results..Clinical Benefits..Apixaban..Direct Evidence: Apixaban versus Warfarin..In the ARISTOTLE trial, patients receiving apixaban had a lower rate of stroke/SE (1.27% per year) compared to those in the warfarin group (1.6%) (HR: 0.79; 95% CI: 0.66 to 0.95; p=0.02). Risk of MI with apixaban was not statistically significantly different from that with warfarin (HR: 0.88; 95% CI: 0.66 to 1.17; p=0.37). The rate of all-cause mortality was lower in the apixaban group compared to the warfarin group (HR: 0.89; 95% CI: 0.80 to 0.998; p=0.047).(2) ..Indirect Evidence: Apixaban versus Dabigatran ..Tables 3.2 and 3.3 provide point estimates of the relative effect of apixaban and rivaroxaban versus dabigatran and warfarin for the NMA outcomes. Risk of stroke/SE with apixaban was not statistically significantly different from that with dabigatran (HR: 1.2; 95% CrI: 0.9 to 1.59). In contrast, apixaban was more efficacious than dabigatran in reducing MI (HR: 0.64; 95% CrI: 0.41 to 0.98). There was no difference in all-cause mortality (HR: 1.01; 95% CrI: 0.85 to 1.2)...Rivaroxaban..Direct Evidence: Rivaroxaban versus Warfarin..In the ROCKET AF trial, patients receiving rivaroxaban had a lower rate of stroke/SE (1.7% per year) compared to those in the warfarin group (2.2%) (HR: 0.79; 95% CI: 0.66 to 0.96; p=0.02). The risk of MI and all-cause mortality were not statistically significantly lower, but the point estimates favored rivaroxaban (MI HR: 0.81; 95% CI: 0.63 to 1.06; p=0.12; mortality HR: 0.85; 95% CI: 0.70 to 1.02; p=0.07). ..Indirect Evidence: Rivaroxaban versus Dabigatran ..The risk of stroke/SE with rivaroxaban was not statistically significantly different from that with dabigatran (HR: 1.2; 95% CrI: 0.89 to 1.6); however, the risk of MI was lower (HR: 0.59; 95% CrI: 0.38 to 0.9). There was no statistically significant difference in all-cause mortality (HR: 0.97; 95% CrI: 0.77 to 1.21)...All other outcomes are reported in Supplement D.(1) ..Harms..Apixaban ..In the ARISTOTLE trial, the rate of major bleeding was lower in the apixaban group compared to the warfarin group (2.13% vs. 3.09% per year, HR: 0.69; 95% CI: 0.60 to 0.80; p<0.001), as was intracranial bleeding (HR: 0.42; 95% CI: 0.30 to 0.58), though absolute rates were small.(2) Estimates from the NMA reported that the risk of major bleeding was lower with apixaban compared to dabigatran (HR: 0.74; 95% CrI: 0.61 to 0.91), but there was no difference for intracranial bleeding (HR: 1.05; 95% CrI: 0.63 to 1.77). See Table 3.5 and Supplement Table D2.5...Patients in the apixaban arm of ARISTOTLE were less likely to discontinue the study drug (Table 3.4), but the absolute difference was small. Results of the NMA showed that apixaban had lower total discontinuation and discontinuation due to AEs compared to dabigatran (Supplement Tables D2.9 and D2.10)...Rivaroxaban ..In the ROCKET AF trial, the rate of major bleeding was similar in the rivaroxaban and warfarin groups. Patients receiving rivaroxaban had a lower rate of intracranial bleeding (HR: 0.67; 95% CI: 0.47 to 0.93), though absolute rates were small.(3) The NMA

Question	Sub-Question
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	<p>Response</p> <p>results for rivaroxaban versus dabigatran showed no statistically significant difference in major bleeding (HR: 1.12; 95% CrI: 0.92 to 1.37) or intracranial bleeding (HR: 1.67; 95% CrI: 0.99 to 2.82)...Patients in the rivaroxaban arm of ROCKET AF were more likely to discontinue the study drug and discontinue due to AEs compared with warfarin, though the absolute differences were small. The NMA results for rivaroxaban versus dabigatran showed lower rates for total discontinuation and discontinuation due to AEs for rivaroxaban...See Supplement D for additional NMA results for harms and discontinuation.(1)..Observational Data..Two large high-quality observational studies were identified that examined long-term safety and effectiveness of apixaban and rivaroxaban.(4-6) These studies used propensity scoring to account for confounding, and are described in detail in Supplement D...Findings in Lau et al. (N=527,226) comparing both drugs to dabigatran in a multinational sample (US, UK, France, and Germany) were generally similar to those in our NMAs with the following exceptions (4):</p> <ul style="list-style-type: none"> • Lower relative major gastrointestinal bleeding risk with apixaban (HR: 0.81; 95% CI: 0.70 to 0.94) • Higher relative point estimates for all-cause mortality with apixaban (HR: 1.22; 95% CI: 0.94 to 1.60) and with rivaroxaban (HR: 1.16; 95% CI: 0.89-1.59), although these were non-significant with relatively wide confidence intervals. • Higher relative major gastrointestinal bleeding risk with rivaroxaban (HR: 1.15; 95% CI: 1.04 to 1.28) <p>Findings in Chan et al. (N=106,044) comparing both drugs to warfarin in a Taiwanese sample found both apixaban and rivaroxaban were associated with a significantly higher risk of interstitial lung disease (ILD) compared to warfarin, though the absolute risk was low (0.29 per 100 person years with DOACs, 0.17 per 100 person years with warfarin).(5) Observational studies cannot prove causality, but ILD cannot be ruled out as a potential rare complication of DOACs. ..Findings from Graham et al. (N=134,414) comparing dabigatran and warfarin (comparators of interest) in a sample of Medicare patients are reported in the supplement.(1, 6)..Uncertainty and Controversies..Indirect analyses were necessary to compare apixaban and rivaroxaban to dabigatran. This increases the uncertainty in the findings. Our NMA results are similar to those observed in the large observational study identified that compares the DOACs, increasing our confidence in the results.(4)..Patients enrolled in the RCTs had some baseline differences compared to a Medicare population. Those in the RCTs had had higher rates of heart failure, prior stroke, and MI, and patients in ARISTOTLE and RE-LY were slightly younger than a Medicare population as these trials included patients under age 65.(7)..Uncertainties regarding findings for key patient subgroups are discussed in Section 4...3.2.3. Summary and Comment - Comparative Clinical Effectiveness..Summary evidence ratings are shown in Table 3.6. For apixaban, we rated the evidence on comparative clinical effectiveness as demonstrating a high certainty of a small net benefit compared with warfarin (B rating). In the pivotal randomized trial there were statistically significant benefits for apixaban in preventing strokes/systemic embolism and major bleeding, but the absolute differences were small. There was also a small, but non-significant trend towards lower total mortality. There were no important differences in adverse events or discontinuation rates. In addition, apixaban has the</p>
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Question	Sub-Question
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Question	Sub-Question	Response
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Question	Sub-Question	Response
		<p>advantage of not requiring regular laboratory monitoring and dose adjustments that are required for safe and effective use of warfarin...We judged the evidence on apixaban versus dabigatran to demonstrate moderate certainty of a comparable or small net benefit (C+ rating). There were no randomized trials directly comparing the two therapies, and in our network meta-analyses, there was no significant difference in the prevention of strokes/systemic embolism. There was a small, but statistically significant reduction in major bleeding, a finding also noted in a large, observational real-world study. There were no important differences in adverse events or discontinuation rates...For rivaroxaban versus warfarin, the evidence was rated as demonstrating high certainty of a small net benefit (B rating). The pivotal randomized trial showed small, but significant benefits in the prevention of strokes/systemic embolism and major bleeding. There was also a small, but non-significant trend towards lower total mortality. There were no important differences in adverse events or discontinuation rates, and rivaroxaban has the advantage of not requiring regular laboratory monitoring and dose adjustments that are required for safe and effective use of warfarin...For rivaroxaban versus dabigatran, however, we judge the evidence provides high certainty of only a comparable net benefit (C rating). In our network meta-analyses, there were no significant differences in the prevention of strokes/systemic embolism, bleeding rates, or total mortality. Furthermore, our decision-analytic model found the differences between the two DOACs in life-years and evLYs were near zero. In addition, in a large observational real-world study the bleeding rates for rivaroxaban and dabigatran were similar.(2)..3.3. Comparative Effectiveness and Cost</p>

Question	Sub-Question	Response
		<p>..3.3.1. Methods Overview..We developed a de novo decision-analytic model to assess the lifetime health outcomes and costs of apixaban and rivaroxaban relative to warfarin and dabigatran. If desired, ICER can provide an executable model file to CMS. Health outcomes included cardiovascular events (i.e., number of strokes, MIs, and major bleeds), life years, and equal value life years (evLYs). Importantly, evLYs are a measure of health that captures the impact of treatment on both length of life and quality of life while weighing the value of extended life of all individuals in exactly the same way. In doing so, the evLY eliminates any risk of valuing extended life lower for conditions in which people are elderly, disabled, or terminally ill. Additional details on the evLY are presented in Section 2.2. ..All patients in the model had NVAf and could be in a health state of "well," chronic post-stroke (ischemic and hemorrhagic), chronic post-MI, or death. Acute events including stroke, MI, and major bleeds (intracranial hemorrhage [ICH], gastrointestinal [GI], and other) were captured as transient events within all living health states. Patients experiencing a stroke or MI who survived the event transitioned to a chronic health state with quality-of-life decrements and incurred costs reflective of individuals experiencing a prior stroke or MI. Patients in the post-stroke state were at risk of subsequent strokes and other events (except MI) and remained in the post-stroke state until they died. Patients in the post-MI state were at risk of subsequent MIs and other events and remained in that state unless they died or experienced a stroke. All patients could transition to death from all causes (including background and NVAf-specific mortality) from any of the alive health states. In addition, patients could die from acute events (stroke, MI, major bleeds). Health outcomes and costs were discounted at 3% per year...Key model inputs included clinical event probabilities, quality of life values, and health care costs. Where available, Medicare-specific</p>

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Question	Sub-Question
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costs based on the Agency for Healthcare Research and Quality's (AHRQ) Healthcare Cost and Utilization Project (HCUP) were used. Productivity changes and other non-intervention indirect costs were included in a modified societal perspective analysis. Treatment effectiveness was estimated using findings from the clinical review, informed by a network meta-analysis. ..The model included non-intervention health care sector costs, including chronic NVAf-related condition costs, acute cardiovascular event-related costs, and chronic condition costs for post-stroke and post-MI-related care. Generic versions of dabigatran were first launched in the US in 2022.(8) Because of the recency of launch, no stable data on the effective Medicare price for dabigatran are available publicly. The model results therefore are framed as price premiums and, as such, can be informative regardless of the prices CMS determines are paid by Medicare for warfarin and dabigatran. For the same reason, and because the direction of the treatment efficacy varies by cardiovascular event, the presented model results do not include a cost-consequence analysis (e.g., cost per stroke averted). ..Detailed methods and results are presented in the Supplement.(1)..3.3.2. Results..Projected Discounted Lifetime Health Outcomes and Non-Intervention Healthcare Sector Costs for Apixaban and Rivaroxaban versus Warfarin and Dabigatran..Total lifetime discounted health outcomes and non-intervention health care sector costs (inclusive of acute event and chronic condition costs) for each intervention and comparator are shown in Table 3.7. .Apixaban versus Warfarin..Compared to warfarin, apixaban resulted in fewer strokes, MIs, and major bleeds. Overall, apixaban resulted in more life years and evLYs gained and lower non-intervention health care sector costs..Apixaban versus Dabigatran..Compared to dabigatran, apixaban resulted in fewer MIs and major bleeds, and a greater number of strokes. Overall, apixaban resulted in more life years and evLYs gained and lower non-intervention health care sector costs over the lifetime of the model. ..Rivaroxaban versus Warfarin..Compared to warfarin, rivaroxaban resulted in fewer strokes and MIs, and a greater number of major bleeds. Overall, rivaroxaban resulted in more life years and evLYs gained, and lower non-intervention health care sector costs over the lifetime of the model...Rivaroxaban versus Dabigatran..Compared to dabigatran, rivaroxaban resulted in fewer MIs and a higher number of strokes and major bleeds. Overall, rivaroxaban resulted in the same life years and evLYs gained, with marginally lower non-intervention health care sector costs over the lifetime of the model. ..Price Premium Threshold Analyses..We framed our price threshold calculations as the price premiums for apixaban and for rivaroxaban over whatever the annualized price paid for warfarin and dabigatran may be (Table 3.9). Considering a range of cost-effectiveness thresholds is recommended, and the most commonly suggested thresholds in the US are \$100,000 and \$150,000 per QALY.(9, 10) We used these same thresholds when substituting the evLYG for the QALY, which would have the effect of increasing the premium prices at each threshold. We have included a wider range of thresholds to provide CMS with additional pricing points for consideration. ..Since CMS may want to consider comparative results for apixaban and rivaroxaban versus both warfarin and dabigatran, we present threshold price results versus both these potential comparators. The results are incremental to the price of the comparator agent, and as such, the results remain relevant regardless of whatever price CMS might pay for warfarin or dabigatran. ..Annual price premiums are shown in Table 3.9. Thirty-day price premiums above warfarin and



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dabigatran pricing can be calculated by dividing the annualized price by 12.175. For apixaban, calculated annual price premiums relative to the cost to CMS of warfarin are \$1,260 at a threshold of \$50,000/evLYG; \$2,290 at \$100,000/evLYG; \$3,320 at \$150,000/evLYG; and \$4,350 at \$200,000/evLYG. Annual price premiums for apixaban relative to dabigatran are: \$240 at \$50,000/evLYG; \$340 at \$100,000/evLYG; \$430 at \$150,000/evLYG; and \$530 at \$200,000/evLYG...For rivaroxaban, annual price premiums relative to the cost to CMS of warfarin are \$1,110 at a threshold of \$50,000/evLYG; \$2,050 at \$100,000/evLYG; \$2,980 at \$150,000/evLYG; and \$3,920 at \$200,000/evLYG. Compared to dabigatran, however, rivaroxaban was not associated with health gains, and therefore decision analytic modeling confirmed that the evidence does not support a price premium for rivaroxaban above CMS pricing for dabigatran...Uncertainty and Controversies..No measure of health gain, including individual cardiovascular events or summary measures such as the evLYG, captures all information important in value considerations. Additional considerations such as unmet need are relevant to consider in discussions on value and pricing negotiations...We recognize that quality of life associated with acute cardiovascular events and their longer-term sequelae vary across individual patients. Our modeling approach aggregates these impacts to find an average projected lifetime benefit to inform threshold pricing estimates. Given that CMS is seeking a single price for consideration as an initial offer, it is reasonable for an aggregated population-based approach to be used. ..No publicly available net price for apixaban and rivaroxaban from the Medicare population was available for our analysis; therefore, we are unable to compare our results to current Medicare prices for these agents. ..Sensitivity Analyses..Deterministic and probabilistic sensitivity analyses were conducted. In the Supplement, we present independent tornado diagrams for incremental non-intervention health care sector costs and incremental evLYGs for each intervention versus warfarin and dabigatran. Based on probabilistic analyses, model findings were robust to uncertainties in parameter estimates...Scenario Analyses..We conducted a scenario analysis from a modified societal perspective which included warfarin monitoring time and associated costs, and costs related to patient and caregiver productivity loss due to illness. The societal perspective analysis is considered “modified” because it does not include broader societal impacts such as effects on education, tax payments or benefits, or environmental impact. The modified societal perspective analysis supported annual value-based price premiums that were approximately \$120 higher for apixaban when compared to dabigatran across the evaluated thresholds; annual value-based price premiums were \$150 higher for rivaroxaban when compared to dabigatran. ..Detailed results from all scenario analyses can be found in the Supplement.(1)..Model Validation..Details related to model validation can be found in the Supplement.(1)..3.3.3. Summary and Comment - Comparative Effectiveness and Cost..We projected lifetime health outcomes and costs for a population of Medicare patients with NVAf receiving apixaban, rivaroxaban, dabigatran, or warfarin. There was an observed health benefit achieved for apixaban and rivaroxaban compared to warfarin, and marginal health gains for apixaban but not for rivaroxaban when compared to dabigatran. The marginal health benefits observed across DOACs is partially explained by the occurrence of competing events. For example, based on the network meta-analysis, dabigatran has a numerically favorable stroke risk profile, and a less favorable MI

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		<p>risk profile compared to apixaban and rivaroxaban. When considering the impact of these events on differences in life years and evLYs (which considers health related quality of life impacts and survival), very similar overall health benefits are observed between DOACs. In addition to the health differences observed, threshold pricing estimates include consideration for the cost-offsets observed between intervention and comparator. ..In summary, both apixaban and rivaroxaban have demonstrated clinical benefits over warfarin that support a range of premium pricing options. Modeling of all health and cost effects showed incremental benefits for apixaban (greater evLYs and lower costs) compared to dabigatran, suggesting that a price premium, albeit marginal, would be reasonable. For rivaroxaban, the modeled health outcomes suggest overall comparable clinical effectiveness versus dabigatran, and as such, reference pricing to dabigatran could be considered a reasonable policy application of the cost-effectiveness findings.</p>
	Hyperlink to Table/Charts/Graphs - Additional Materials for Question 28	
	Evidence Submitted include a cost-effectiveness measure?	N
Question 29: Comparative Effectiveness on Specific Populations	What type of Evidence is shown?	N
	Response to Question 29	<p>4.1. Comparative Clinical Effectiveness – Subgroup Analyses and Heterogeneity..To evaluate subgroups of interest and heterogeneity, we evaluated subgroup analyses conducted in the three main trials reported in the response to question 28 and one observational study from Lau et al.(1) Subgroup analyses for the RE-LY trial, comparing dabigatran and warfarin, are reported in the Supplement.(2) We also identified two trials that specifically enrolled patients with NVAf and end-stage renal disease (ESRD).(3, 4) Ultimately, there are no persuasive findings in the clinical evidence of major differences in the balance of risks and benefits for patients with ESRD, the elderly, or those with terminal illness (e.g., cancer). There is currently no reported evidence that examined differences in risk and benefits for children or those with disabilities. The studies are described in detail below...4.1.1. End-Stage Renal Disease..Comparative Clinical Effectiveness - Trials in Patients with ESRD..Evidence informing our review of the interventions of interest in those with ESRD were derived from two Phase IV clinical trials: RENAL AF and Valkyrie.(3, 4) Both ESRD trials were small and underpowered to detect comparative efficacy of the intervention of interest versus the comparator. Overall, there are no persuasive findings in the clinical evidence to suggest major differences in the balance of risks and benefits for patients with ESRD. The studies are described in detail below. ..RENAL AF was a Phase IV open-label, blinded-outcome RCT that evaluated the efficacy of oral apixaban 5 mg twice daily (2.5 mg twice daily if weight ≤ 60 kg or age ≥</p>

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80 years) versus warfarin (INR 2-3) in those with AF and ESRD in the US.(3) RENAL AF was designed to test for noninferiority on the primary outcome (major or clinically relevant nonmajor bleeding) and superiority for primary and secondary outcomes, including stroke/SE and death. There were challenges with participant recruitment and this study was ultimately terminated early, which meant that the study was underpowered to detect a statistical effect. Patients were followed for a median of 330 (apixaban) or 340 (warfarin) days. See Supplement D2 for further description of the planned analysis and termination. Full inclusion and exclusion criteria for both ESRD trials are described in Supplement Table D3.1., and baseline characteristics are outlined in Table 4.1. and Supplement Table D3.30. Like ARISTOTLE, a greater proportion of patients were younger (37% were <65 years of age). Patients were more racially diverse (45% identified as Black) and were more likely to have heart failure, hypertension, and diabetes as compared to the three RCTs and the other ESRD trial. ..Rates of stroke, SE, and bleeding-related mortality were similar among those in the apixaban or warfarin group at one year.(3) In contrast, rates of major or non-major clinically relevant bleeding were high overall and numerically higher in the apixaban group (32%) versus warfarin group (26%) as was all-cause mortality (26% vs. 18% in apixaban versus warfarin, respectively). See Supplement Tables D3.31 and D3.32. However, due to the small sample size (N=154), the authors were not able to draw any conclusions from the clinical data. ..Valkyrie was a Phase IV open-label RCT that evaluated the efficacy of oral rivaroxaban 10 mg once daily versus warfarin (INR 2-3) in those with NVAf on chronic hemodialysis.(4) There was an additional group who received rivaroxaban and menquinone-7 (MK-7). As this intervention was not one of our interventions of interest, we did not include the results of this group in our analysis. The study was designed to examine whether the replacement of warfarin by rivaroxaban can slow progression of vascular calcification. Thus, the primary outcome was the absolute and relative change in coronary artery calcification score. Secondary outcomes included a composite of non-fatal stroke and cardiovascular events, death, and bleeding at a median of 1.8 years. Compared to the RCTs, patients were older with a median age of 80, were more likely to have had a prior stroke or MI, and had a higher CHA2DS2-VAS score; although the mean was comparable to the ROCKET AF trial. ..The primary clinical endpoint for the Valkyrie study was a composite of fatal cardiovascular disease and nonfatal stroke, cardiac events, and other vascular events at a median of 1.8 years. The rate of the composite outcome was significantly lower in the rivaroxaban compared to the warfarin group (HR: 0.34; 95% CI: 0.19 to 0.61; p=0.0003).(5) The rate of all-cause death and any bleeding events was numerically lower in the rivaroxaban group compared to the warfarin group. Stroke did not differ between the groups. See Supplement Table D3.31. Major bleeding outcomes were only available for the two rivaroxaban groups combined (rivaroxaban alone and rivaroxaban plus vitamin K2). Like RENAL AF, the study was not powered to detect clinical benefit and thus results of these two ESRD trials should be interpreted with caution...As noted above, both ESRD trials were small and underpowered to detect comparative efficacy of the intervention of interest versus the comparator. There are no persuasive findings in the clinical literature suggesting major differences in the overall balance of risks and benefits for patients with ESRD...Within-Trial Subgroups for ESRD..Within-trial subgroup analyses examined the effect of renal function or chronic kidney disease, as a

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proxy for ESRD, on treatment benefit. There were no consistent subgroup effects for renal function. This was especially true when using a continuous assessment of renal function, which may be considered a more sensitive variable than a categorical assessment...There was no effect modification by renal function reported across subgroup analyses of stroke/SE, MI, or all-cause mortality of the ARISTOTLE trial.(6-9) See Supplement Tables D3.5-6, and D3.11-12. There was a suggestion of a greater reduction in major bleeding in patients with moderate or severe renal impairment (creatinine clearance [CrCl] ≤ 50 mL/min) in those who received apixaban versus warfarin (p value for interaction = 0.03).(6) In a subsequent analyses of those with advanced chronic kidney disease (CrCl 25 to 30 mL/min), there were fewer major bleeding events in those in the apixaban group, compared to warfarin, but no difference in intracranial bleeding.(7) However, a secondary data analysis that used worsening renal function as a continuous independent variable reported no effect modification by renal function on any of the outcomes.(8) Renal function as a continuous variable could be considered a more sensitive measure to examine treatment modification and overcomes the issue of interpreting different categories of renal function that have been used across analyses...Differences in results when using categories versus continuous variables were also found in subgroup analyses of the ROCKET AF trial. In several analyses that categorized patients into renal function groups (e.g., 30-49, > 50 ; or < 50 , 50-80, > 80 CrCl mL/min), there was no interaction between renal function and treatment group for major or non-major bleeding, major bleeding alone, stroke/SE, and ischemic or hemorrhagic stroke.(10-12) However, when median CrCl was used as a variable, Piccini et al. (2014) reported that those in the warfarin group who had a major bleed had lower CrCl at baseline as compared to patients in the rivaroxaban group.(13) This effect modification was not replicated by Fordyce et al. (2016).(14) Fordyce et al. identified patients who experienced a worsening of renal function during the study ($> 20\%$ decrease in CrCl from screening to any point in the trial) and reported no treatment modification by worsening renal function for any bleeding, MI, or death. However, those who had worsening renal function and were given rivaroxaban had a larger reduction in stroke/SE compared to those given warfarin (HR: 0.50; 95% CI: 0.27 to 0.93; $p=0.05$). See Supplement Tables D3.15, D.17, and D3.21-D3.25. The subgroup analyses from this trial were inconsistent. There are also issues with interpretation when including independent variables that change over the course of a study (e.g., worsening renal function) as it is unclear how the intervention or other uncontrolled factors in the trial may influence this relationship. ..The observational study from Lau et al. (2022) examined the primary endpoint (stroke/SE) and safety endpoints (bleeding and all-cause mortality) in patients with chronic kidney disease (CKD) for the comparisons of interest (apixaban versus dabigatran; dabigatran versus rivaroxaban).(1) See Supplement Table D3.39. Consistent with the overall sample of the Lau et al. study, the authors reported similar rates of stroke/SE, intracranial hemorrhage, and all-cause mortality in those with CKD. For GI bleeding, the findings were consistent with the overall sample for the apixaban versus dabigatran comparison. However, when comparing dabigatran versus rivaroxaban, the rates of GI bleeding were similar in those with CKD, suggesting less benefit from dabigatran in reducing GI bleeding in those with CKD. The authors note that apixaban may be more favorable in reducing the risk of GI bleeding in those with CKD...4.1.2. Individuals with Disabilities..No reported evidence examined

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the efficacy and safety of the interventions of interest in individuals with disabilities with NVAf. ..4.1.3. The Elderly..Within-trial subgroup analyses examined the effect of age on treatment benefit. There were no clear subgroup effects by age, except a potential signal for lower risk of extracranial bleeding, particularly GI bleeding, in older adults prescribed DOACs as compared to warfarin. ..There was no effect modification by age reported across multiple analyses of primary and secondary outcomes from the ARISTOTLE trial.(6, 15) See Supplement Tables D3.5, D3.6, and D3.13. ..In the main trial publication, there was no effect modification by age for stroke/SE nor major bleed in the ROCKET AF trial, which was confirmed in a secondary analysis.(10, 12) Additional secondary data analyses reported that there was no treatment modification for major bleeding, fatal bleeding, and intracranial hemorrhage alone.(12, 16) However, when examining major and non-major clinically relevant bleeding, there was a significant effect modification by age ($p=0.009$).(12) There was a higher risk of bleeding in those 75 years and older in the rivaroxaban group versus warfarin (HR: 1.13; 95% CI: 1.02 to 1.25) but, in those less than 75 years, there was no significant difference in the bleeding risk between the groups (HR: 0.93; 95% CI: 0.84 to 1.04). See Supplement Tables D3.15-20 and D3.24. Given these results, it is likely that the subgroup effect, if real, may be driven by non-major clinically relevant bleeding and, as noted in the study, extracranial bleeding. Gastrointestinal bleeding was more common in those over 75 years in the rivaroxaban group as compared to the warfarin group. ..The observational study conducted by Lau et al. (2022) examined the effect of age in the comparisons of interest.(1) Similar to the subgroup analyses for CKD, the results for stroke/SE, intracranial hemorrhage, and all-cause mortality in those 80 years or older were consistent with the overall sample. See Supplement Table D3.40. Again, the rates of GI bleeding were similar in those 80 years or older when comparing dabigatran versus rivaroxaban, inconsistent with the overall sample. The authors noted that apixaban may be more favorable in reducing the risk of GI bleeding for older adults...4.1.4. Individuals Who Are Terminally Ill..A within-trial subgroup analysis of the ARISTOTLE trial examined the efficacy and safety of apixaban versus warfarin in those with AF and active cancer ($N=157$), history of (remote) cancer ($N=1,079$), or no cancer ($N=16,947$).(17) Those with active or remote cancer were older (74 vs. 70) and had a slightly higher CHA2DS2-VASc score compared to those with no cancer. Those with active cancer had a higher rate of all-cause mortality compared to those with no or remote cancer. See Supplement Tables D3.7 to D3.9. When examining the effect on the primary efficacy and safety outcomes for apixaban versus warfarin according to cancer status, the results were consistent in patients with and without cancer. Apixaban versus warfarin was associated with fewer thrombotic events in patients with active cancer (HR: 0.30; 95% CI: 0.11 to 0.83) compared to those with no cancer (HR: 0.86; 95% CI: 0.78 to 0.95). There was also a trend towards greater reduction in mortality with apixaban versus warfarin in those without cancer. With further investigation, the authors noted that this effect was mostly driven by high rates of non-cardiovascular death in those with remote cancer who received apixaban versus those treated with warfarin. ..4.1.5. Children..No reported evidence examined the efficacy and safety of the interventions of interest in children with NVAf...Subgroups for the RE-LY trial are reported in Section D5 of the Supplement.(2) ..4.2 Subgroup Uncertainties and Controversies..There are uncertainties around the comparative effectiveness of

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		<p>the drugs in patients with ESRD. Both trials in this patient population were underpowered: one because it was a pilot study and the other stopped enrolling patients due to challenges in recruitment. However, an individual patient-level NMA that combined the results of four trials including the three in our NMA found that the DOACs were safer and more effective than warfarin in patients with NVAf at 5 levels of renal function down to a creatine clearance of 25-29.9 ml/min.(18) Dabigatran is renally cleared with dose reduction indicated for patients with a creatine clearance of 15-30 ml/min.(19).Older patients are a major subgroup of interest as they comprise most patients covered by Medicare. As noted above, there was no evidence of effect modification by age in any of the randomized trials included in our analyses. In addition, an individual patient-level NMA that combined the results of four trials including the three in our NMA found that the DOACs were safer and more effective than warfarin in patients without effect modification by age (<65, 65-75, and >75 years) for the outcomes of stroke / systemic embolism, major bleeding, and total mortality.(20)..4.2 Comparative Cost Effectiveness – Subgroup Analyses..There was no clinical evidence to support subgroup analyses within the cost-effectiveness model.</p> <ol style="list-style-type: none">1. Lau WCY, Torre CO, Man KKC, Stewart HM, Seager S, Van Zandt M, et al. Comparative Effectiveness and Safety Between Apixaban, Dabigatran, Edoxaban, and Rivaroxaban Among Patients With Atrial Fibrillation : A Multinational Population-Based Cohort Study. Ann Intern Med. 2022;175(11):1515-24. Epub 2022/11/01. doi: 10.7326/m22-0511. PubMed PMID: 36315950.2. Tice JA, Richardson M, Wright A, Seidner M, Rind DM, Pearson SD. Special Assessment to Inform CMS Drug Price Negotiation: Eliquis and Xarelto - Supplemental Materials: Institute for Clinical and Economic Review; 2023 [cited 2023 October 2]. Available from: https://icer.org/wp-content/uploads/2023/09/ICER_NVAf_Medicare_Supplement_100223.pdf.3. Pokorney SD, Chertow GM, Al-Khalidi HR, Gallup D, Dignacco P, Mussina K, et al. Apixaban for Patients With Atrial Fibrillation on Hemodialysis: A Multicenter Randomized Controlled Trial. Circulation. 2022;146(23):1735-45. doi: 10.1161/CIRCULATIONAHA.121.054990.4. De Vriese AS, Caluwé R, Pyfferoen L, De Bacquer D, De Boeck K, Delanote J, et al. Multicenter Randomized Controlled Trial of Vitamin K Antagonist Replacement by Rivaroxaban with or without Vitamin K2 in Hemodialysis Patients with Atrial Fibrillation: the Valkyrie Study. Journal of the American Society of Nephrology. 2020;31(1).5. De Vriese AS, Caluwé R, Van Der Meersch H, De Boeck K, De Bacquer D. Safety and Efficacy of Vitamin K Antagonists versus Rivaroxaban in Hemodialysis Patients with Atrial Fibrillation: A Multicenter Randomized Controlled Trial. Journal of the American Society of Nephrology. 2021;32(6).6. Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus Warfarin in Patients with Atrial Fibrillation. New England Journal of Medicine. 2011;365(11):981-92. doi: 10.1056/NEJMoa1107039.
	Hyperlink to Citation - Additional Materials for Question 29	

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| | | <p>7. Stanifer JW, Pokorney SD, Chertow GM, Hohnloser SH, Wojdyla DM, Garonzik S, et al. Apixaban Versus Warfarin in Patients With Atrial Fibrillation and Advanced Chronic Kidney Disease. <i>Circulation</i>. 2020;141(17):1384-92. doi: doi:10.1161/CIRCULATIONAHA.119.044059.</p> <p>8. Hijazi Z, Hohnloser SH, Andersson U, Alexander JH, Hanna M, Keltai M, et al. Efficacy and Safety of Apixaban Compared With Warfarin in Patients With Atrial Fibrillation in Relation to Renal Function Over Time: Insights From the ARISTOTLE Randomized Clinical Trial. <i>JAMA Cardiology</i>. 2016;1(4):451-60. doi: 10.1001/jamacardio.2016.1170.</p> <p>9. Hohnloser SH, Hijazi Z, Thomas L, Alexander JH, Amerena J, Hanna M, et al. Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial. <i>European Heart Journal</i>. 2012;33(22):2821-30. doi: 10.1093/eurheartj/ehs274</p> <p>10. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation. <i>New England Journal of Medicine</i>. 2011;365(10):883-91. doi: 10.1056/NEJMoa1009638.</p> <p>11. Fox KAA, Piccini JP, Wojdyla D, Becker RC, Halperin JL, Nessel CC, et al. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment. <i>European Heart Journal</i>. 2011;32(19):2387-94. doi: 10.1093/eurheartj/ehr342.</p> <p>12. Halperin JL, Hankey GJ, Wojdyla DM, Piccini JP, Lokhnygina Y, Patel MR, et al. Efficacy and Safety of Rivaroxaban Compared With Warfarin Among Elderly Patients With Nonvalvular Atrial Fibrillation in the Rivaroxaban Once Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF). <i>Circulation</i>. 2014;130(2):138-46. doi: 10.1161/CIRCULATIONAHA.113.005008.</p> <p>13. Piccini JP, Garg J, Patel MR, Lokhnygina Y, Goodman SG, Becker RC, et al. Management of major bleeding events in patients treated with rivaroxaban vs. warfarin: results from the ROCKET AF trial. <i>European Heart Journal</i>. 2014;35(28):1873-80. doi: 10.1093/eurheartj/ehu083.</p> <p>14. Fordyce CB, Hellkamp AS, Lokhnygina Y, Lindner SM, Piccini JP, Becker RC, et al. On-Treatment Outcomes in Patients With Worsening Renal Function With Rivaroxaban Compared With Warfarin. <i>Circulation</i>. 2016;134(1):37-47. doi: 10.1161/CIRCULATIONAHA.116.021890.</p> <p>15. Halvorsen S, Atar D, Yang H, De Caterina R, Erol C, Garcia D, et al. Efficacy and safety of apixaban compared with warfarin according to age for stroke prevention in atrial fibrillation: observations from the ARISTOTLE trial. <i>European Heart Journal</i>. 2014;35(28):1864-72. doi: 10.1093/eurheartj/ehu046.</p> <p>16. Goodman SG, Wojdyla DM, Piccini JP, White HD, Paolini JF, Nessel CC, et al. Factors Associated With Major Bleeding Events: Insights From the ROCKET AF Trial (Rivaroxaban Once-daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation). <i>Journal of the American College of Cardiology</i>. 2014;63(9):891-900. doi: https://doi.org/10.1016/j.jacc.2013.11.013.</p> |
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		<p>17. Melloni C, Dunning A, Granger CB, Thomas L, Khouri MG, Garcia DA, et al. Efficacy and Safety of Apixaban Versus Warfarin in Patients with Atrial Fibrillation and a History of Cancer: Insights from the ARISTOTLE Trial. The American Journal of Medicine. 2017;130(12):1440-8.e1. doi: 10.1016/j.amjmed.2017.06.026.</p> <p>18. Harrington J CA, Hua K, Wallentin L, Patel MR, Hohnloser SH, Giugliano RP, Fox KA, Hijazi Z, Lopes RD, Pokorney SD. . Direct Oral Anticoagulants Versus Warfarin Across the Spectrum of Kidney Function: Patient-Level Network Meta-Analyses From COMBINE AF. Circulation. 2023;147(23):1748-57.</p> <p>19. U.S. Food and Drug Administration. PRADAXA® (dabigatran etexilate) Package Insert. 2021.</p> <p>20. Carnicelli AP HH, Connolly SJ, Eikelboom J, Giugliano RP, Morrow DA, Patel MR, Wallentin L, Alexander JH, Cecilia Bahit M, Benz AP. Direct oral anticoagulants versus warfarin in patients with atrial fibrillation: patient-level network meta-analyses of randomized clinical trials with interaction testing by age and sex. Circulation. 2022;145(4):242-55.</p>
	<p>Hyperlink to Table/Charts/Graphs - Additional Materials for Question 29</p> <p>Evidence Submitted include a cost-effectiveness measure?</p> <p>What type of Evidence is shown?</p>	<p>N</p>
Question 30: Addressing Unmet Medical Needs	Response to Question 30	<p>2.1. Qualitative Discussion..Revised guidance from CMS defines unmet need as “treating a disease or condition in cases where no other treatment options exist or existing treatments do not adequately address the disease or condition.”(1) DOACs improve outcomes in NVAf compared with warfarin as they generally provide better protection against stroke and systemic embolism for a similar bleeding risk or equivalent protection with a lower bleeding risk. For most patients, warfarin presents more burdens than DOACs, including the requirement for close laboratory monitoring, particularly at initiation. For many patients ongoing monitoring is required every few weeks. Warfarin also requires that patients adhere to a diet with a consistent intake of vitamin K, and initiation or discontinuation of many other medications will require a new phase of close laboratory monitoring and adjustment of warfarin dosing...Even with the DOACs, however, all patients face a residual risk of strokes and systemic emboli, and all have risks of bleeding events ranging from minor to catastrophic...2.1.1. Patient and Caregiver Perspectives..Patients told us that they did not like having to go to the laboratory at least once a month to monitor their INR when on warfarin. They also expressed frustration at limiting their intake of leafy green vegetables. Taking a pill once or twice a day without laboratory or dietary</p>

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monitoring is much easier. However, for all four drugs, patients complained about bleeding, including unsightly bruises arising without trauma and prolonged bleeding after minor cuts. Some patients live in fear of more significant bleeding, leading them to limit activities (e.g., soccer, skiing, biking) that they had previously enjoyed but which now were felt to pose too great a risk. One patient told us about repeated emergency room visits at which he would urinate blood and blood clots due to complications arising from his prior radiation therapy for prostate cancer. Finally, we heard about the fear of having a stroke with its risk of long-term disability and loss of independence. Patients are aware that none of the available drugs are 100% effective at preventing strokes...

2.2 Quantitative Discussion..Decision-analytic models, often used to support estimates of value-based drug pricing, can also produce quantitative findings on unmet need. Calculations of proportional and absolute health “shortfall” are two different ways to estimate the reduction in lifetime health due to a condition compared with health in the age- and sex-matched general US population. Using the decision-analytic model described in Section 3.3, we calculated proportional and absolute shortfalls in health using the equal value of life years (evLY) measure.(2)..CMS revised guidance states: ..CMS requires respondents submitting information to indicate whether their submission contains information from studies that use measures that treat extending the life of an individual who is elderly, disabled, or terminally ill as of lower value than extending the life of an individual who is younger, nondisabled, or not terminally ill. CMS also requests that respondents submitting information under 1194(e)(2) provide a short description of any cost-effectiveness measures included in the research they are submitting, and how they believe the data avoids treating extending the life of an individual who is elderly, disabled, or terminally ill as of lower value than extending the life of an individual who is younger, nondisabled, or not terminally ill. ..We attest that all measures of health used throughout this submission, and specifically the evLY, do not treat extending the life of an individual who is elderly, disabled, or terminally ill as of lower value than extending the life of an individual who is younger, nondisabled, or not terminally ill. The evLY treats the value of extended life of all individuals in exactly the same way, with each year of life gained from treatment valued identically. As such, the evLY is a nondiscriminatory alternative to the quality-adjusted life year (QALY). The evLY has served for many years as a bedrock of ICER's drug price benchmarks that are used by the Veterans Administration, Medicaid programs, and private insurers. In our public comments on the CMS draft guidance, we provided further rationale for why the evLY is consistent with the IRA and will be helpful to CMS in its deliberations.(3)..To quantify unmet need for patients with NVAf, we present evLY shortfall calculations for two treatments: apixaban and dabigatran. We chose to calculate health shortfalls despite apixaban treatment because it is the market leader in utilization and produced the best lifetime health outcomes in analytic modeling (see Section 3.3). We also chose to calculate health shortfalls for patients treated with dabigatran since those shortfalls represent the “unmet need” for patients not treated with one of the two drugs being negotiated. ..To calculate the absolute evLY shortfall for each condition, we subtracted the lifetime undiscounted evLYs with apixaban treatment from the evLYs expected for the general population (calculated using age- and sex-adjusted estimates for mortality and a constant utility of 0.851 for quality of life). To

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calculate the proportional evLY shortfall, we divided the absolute evLY shortfall by the evLY life expectancy for the general population with the same age and sex distribution at baseline...The undiscounted absolute shortfall for Medicare patients with NVAf treated with apixaban was 2.29 evLYs versus the general age- and sex-adjusted US population. The undiscounted proportional shortfall was $2.29/9.65 = 24\%$. The undiscounted absolute shortfall for Medicare patients with NVAf treated with dabigatran was 2.31 evLYs versus the general age- and sex-adjusted US population. The undiscounted proportional shortfall was $2.31/9.65 = 24\%$. For context, as shown in Table 2.1, the absolute evLY shortfall for Medicare patients with NVAf treated with apixaban is comparable to that observed with osteoporosis but substantially less than with chronic depression or Alzheimer's disease. The proportional shortfall was comparable to that for patients living with ulcerative colitis, but substantially less than for patients with lupus nephritis or relapsing forms of multiple sclerosis.

1. Tice JA, Richardson M, Wright A, Seidner M, Rind DM, Pearson SD. Special Assessment to Inform CMS Drug Price Negotiation: Eliquis and Xarelto - Supplemental Materials: Institute for Clinical and Economic Review; 2023 [cited 2023 October 2]. Available from: https://icer.org/wp-content/uploads/2023/09/ICER_NVAf_Medicare_Supplement_100223.pdf.

2. Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus Warfarin in Patients with Atrial Fibrillation. *New England Journal of Medicine*. 2011;365(11):981-92. doi: 10.1056/NEJMoa1107039.

3. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation. *New England Journal of Medicine*. 2011;365(10):883-91. doi: 10.1056/NEJMoa1009638.

4. Lau WCY, Torre CO, Man KKC, Stewart HM, Seager S, Van Zandt M, et al. Comparative Effectiveness and Safety Between Apixaban, Dabigatran, Edoxaban, and Rivaroxaban Among Patients With Atrial Fibrillation : A Multinational Population-Based Cohort Study. *Ann Intern Med*. 2022;175(11):1515-24. Epub 2022/11/01. doi: 10.7326/m22-0511. PubMed PMID: 36315950.

5. Chan Y-H, Chao T-F, Chen S-W, Lee H-F, Chen W-M, Li P-R, et al. Development of Interstitial Lung Disease Among Patients With Atrial Fibrillation Receiving Oral Anticoagulants in Taiwan. *JAMA Network Open*. 2022;5(11):e2243307-e. doi: 10.1001/jamanetworkopen.2022.43307.

6. Graham DJ, Reichman ME, Wernecke M, Zhang R, Southworth MR, Levenson M, et al. Cardiovascular, Bleeding, and Mortality Risks in Elderly Medicare Patients Treated With Dabigatran or Warfarin for Nonvalvular Atrial Fibrillation. *Circulation*. 2015;131(2):157-64. doi: 10.1161/CIRCULATIONAHA.114.012061.

7. Graham DJ, Baro E, Zhang R, Liao J, Wernecke M, Reichman ME, et al. Comparative Stroke, Bleeding, and Mortality Risks in Older Medicare Patients Treated with Oral Anticoagulants for Nonvalvular Atrial Fibrillation. *Am J Med*. 2019;132(5):596-604.e11. Epub 2019/01/15. doi: 10.1016/j.amjmed.2018.12.023. PubMed PMID: 30639551.

8. IPD Analytics. Cardiovascular: Direct-acting Oral Anticoagulants (DOAC/NOAC). 2023 Contract No.: August 2023.

Hyperlink to Citation -
Additional Materials for
Question 30

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Question	Sub-Question	Response
		<p>9. Sanders GD, Neumann PJ, Basu A, Brock DW, Feeny D, Krahn M, et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. <i>Jama</i>. 2016;316(10):1093-103. Epub 2016/09/14. doi: 10.1001/jama.2016.12195. PubMed PMID: 27623463.</p> <p>10. Neumann PJ, Cohen JT, Weinstein MC. Updating Cost-Effectiveness – The Curious Resilience of the \$50,000-per-QALY Threshold. <i>The New England journal of medicine</i>. 2014;371(9):796-7. doi: 10.1056/NEJMp1405158.</p>
	Hyperlink to Table/Charts/Graphs - Additional Materials for Question 30	
	Evidence Submitted include a cost-effectiveness measure?	Y
	What type of Evidence is shown?	N
Question 31: Patient and Caregiver Experience	Response to Question 31	
Question 32: Executive Summary	Response to Question 32	<p>As a result of the Inflation Reduction Act (IRA), the Centers for Medicare & Medicaid Services (CMS) will soon begin negotiating prices for certain high-expenditure drugs. This submission examines the direct-acting oral anticoagulants (DOACs) apixaban (Eliquis®, Bristol Myers Squibb / Pfizer) and rivaroxaban (Xarelto®, Janssen Pharmaceuticals, Inc.), two of the 10 drugs that CMS has selected for negotiation in the first round. The information in the submission is tailored to reflect legislative specifications in the IRA and subsequent CMS guidance. It is not comprehensive but does include sections on multiple elements related to drug value, providing different options for translating evidence into initial offer prices and for assessing counteroffers from drug makers. We focused on the use of these two drugs for non-valvular atrial fibrillation (NVAf) since that represents the vast majority of use for drugs in this class. As clinical and cost comparators, we selected warfarin, an older generic medication that was the standard therapy for atrial fibrillation prior to the DOACs, and dabigatran, which is the first DOAC available as a generic medication, launched in 2022...We sought patient input and were told of the impact of patients' ongoing fear of having a stroke and the potential for long</p>

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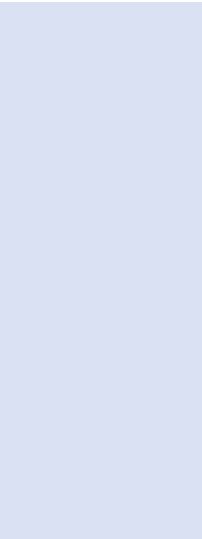
Question	Sub-Question
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Response

term disability and loss of independence. We also heard about their lived experience with bleeding, including the time it takes to stop bleeding after cuts and common unsightly bruises without trauma. Some patients worry continually about more significant bleeding, leading them to limit their activities. As a quantitative measure of unmet need, we found the absolute equal value life years (evLY) shortfall for Medicare patients with NVAf was comparable to that observed with living with osteoporosis but substantially less than with chronic depression or Alzheimer's disease. The proportional evLY shortfall was comparable to that observed with ulcerative colitis, but substantially less than that with lupus nephritis or relapsing forms of multiple sclerosis. ..To estimate the comparative therapeutic impact of apixaban and rivaroxaban in NVAf, we compared each drug to warfarin and to dabigatran. Both apixaban and rivaroxaban had direct randomized controlled trial evidence versus warfarin, but we needed to conduct a network meta-analysis to assess comparisons with dabigatran. This evidence, consistent with results from observational studies, demonstrates that DOACs improve outcomes for patients with NVAf compared to treatment with warfarin. The DOACs generally provide better protection against stroke and systemic embolism for a similar bleeding risk or equivalent protection with a lower bleeding risk. Across the trials, there was no evidence of effect modification by age in any of the outcomes we examined...For apixaban, we have rated the evidence on comparative clinical effectiveness as demonstrating a high certainty of a small net benefit compared with warfarin (B rating). In the pivotal randomized trial there were statistically significant benefits for apixaban in preventing strokes/systemic embolism and major bleeding, but the absolute differences were small. There was also a small, but non-significant trend towards lower total mortality. There were no important differences in adverse events or discontinuation rates. In addition, apixaban has the advantage of not requiring regular laboratory monitoring and dose adjustments that are required for safe and effective use of warfarin...We judged the evidence on apixaban versus dabigatran to demonstrate moderate certainty of a comparable or small net benefit (C+ rating). There were no randomized trials directly comparing the two therapies, and in our network meta-analyses, there was no significant difference in the prevention of strokes/systemic embolism. There was a small, but statistically significant reduction in major bleeding, a finding also noted in a large, observational real-world study. There were no important differences in adverse events or discontinuation rates...For rivaroxaban versus warfarin, the evidence was rated as demonstrating high certainty of a small net benefit (B rating). The pivotal randomized trial showed small, but significant benefits in the prevention of strokes/systemic embolism and major bleeding. There was also a small, but non-significant trend towards lower total mortality. There were no important differences in adverse events or discontinuation rates, and rivaroxaban has the advantage of not requiring regular laboratory monitoring and dose adjustments that are required for safe and effective use of warfarin...For rivaroxaban versus dabigatran, however, we judge the evidence provides high certainty of only a comparable net benefit (C rating). In our network meta-analyses, there were no significant differences in the prevention of strokes/systemic embolism, bleeding rates, or total mortality. Furthermore, our decision-analytic model found the differences between the two DOACs in life-years and evLYs were near zero. In addition, in a large, observational real-world study the bleeding rates for



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Response
rivaroxaban and dabigatran were similar. ..We used decision-analytic modeling to assess the lifetime projected effectiveness and cost of apixaban and rivaroxaban compared to warfarin and dabigatran. Based on their comparative clinical effectiveness, we report price premiums at various cost-effectiveness thresholds for apixaban and rivaroxaban relative to the prices that CMS pays for comparator agents (warfarin and dabigatran) to inform drug price negotiations alongside other considerations. We do not stipulate a specific cost-effectiveness threshold as most appropriate but note for CMS that academic health economics research supports consideration of pricing between \$100,000-\$150,000 per evLYG. ..For apixaban, calculated annual price premiums relative to the cost to CMS of warfarin are \$1,260 at a threshold of \$50,000/evLYG; \$2,290 at \$100,000/evLYG; \$3,320 at \$150,000/evLYG; and \$4,350 at \$200,000/evLYG. Annual price premiums for apixaban relative to dabigatran are: \$240 at \$50,000/evLYG; \$340 at \$100,000/evLYG; \$430 at \$150,000/evLYG; and \$530 at \$200,000/evLYG...For rivaroxaban, annual price premiums relative to the cost to CMS of warfarin are \$1,110 at a threshold of \$50,000/evLYG; \$2,050 at \$100,000/evLYG; \$2,980 at \$150,000/evLYG; and \$3,920 at \$200,000/evLYG. Compared to dabigatran, however, rivaroxaban was not associated with health gains, and therefore decision analytic modeling confirmed that the evidence does not support a price premium for rivaroxaban above CMS pricing for dabigatran.

Table 2.1. Absolute and Proportional evLY Shortfall for Medicare Patients with NVAf Treated with Apixaban Compared to Other Conditions.

	Absolute evLY Shortfall	Proportional evLY Shortfall
Lupus nephritis	22.1	56%
Relapsing remitting multiple sclerosis	18.86	52%
Moderate to severe atopic dermatitis	9.92	28%
Chronic depression	9.65	32%
Ulcerative colitis	6.57	19%
Osteoporosis	2.61	19%
Nonvalvular atrial fibrillation	2.29	24%

evLY: equal-value life year

Table 3.1. Overview of Main Trials

	Arms	Arm size	Study Duration	Baseline Characteristics					
				Age, mean (SD)	% Male	% White	CHADS ₂ , mean (SD)	CHA ₂ DS ₂ -VASc, mean (SD)	HAS-BLED, mean (SD)
ARISTOTLE	Apixaban§	9120	1.8 years*	69.1 (9.61)	64.5	82.6	2.1 (1.1)	3.7 (1.5)	1.8 (1.05)
	Warfarin‡	9081		69.0 (9.74)	65	82.5	2.1 (1.1)	3.7 (1.5)	1.8 (1.06)
ROCKET AF	Rivaroxaban¤	7131	1.6 years*	73 (65-78)†	60.3	82.3	3.5 (0.94)	4.8 (1.3)	2.8 (0.9)
	Warfarin‡	7133		73 (65-78)†	60.3	82.9	3.5 (0.95)	4.8 (1.3)	
RE-LY	Dabigatran**	6076	2 years*	71.5 (8.8)	63.2	70.2	2.2 (1.2)	NR	NR
	Warfarin‡	6022		71.6 (8.6)	63.3	69.8	2.1 (1.1)	NR	NR

AF: atrial fibrillation, CHADS₂: congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), CHA₂DS₂-VASc: congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74 and sex category (female), HAS-BLED: Hypertension, Abnormal liver/renal function, Stroke history, Bleeding history or predisposition, Labile INR, Elderly, Drug/alcohol usage, NR: not reported, SD: standard deviation, %: percent

*median

†median(IQR)

‡INR 2-3 dose

§Apixaban 5mg or 2.5 twice daily

¤Rivaroxaban 20 mg or 15 mg once daily

**Dabigatran 150 mg twice daily

Table 3.2. Network Meta-Analysis Results for Stroke/Systemic Embolism.

Apixaban (5 mg or 2.5 mg BID)			
1 (0.76, 1.31)	Rivaroxaban (20 mg or 15 mg QD)		
1.2 (0.9, 1.59)	1.2 (0.89, 1.6)	Dabigatran (150 mg BID)	
0.79 (0.66, 0.95)	0.79 (0.65, 0.96)	0.66 (0.53, 0.82)	Warfarin (INR: 2-3)

BID: twice a day, QD: once a day.

Legend: Each box represents the estimated hazard ratio and 95% credible interval for the direct and indirect comparisons between two drugs: the drug at the top of the column compared to the drug at the right of the row. Estimates in bold signify that the 95% credible interval does not contain 1.0.

Table 3.3. Network Meta-Analysis Results for Myocardial Infarction.

Apixaban (5 mg or 2.5 mg BID)			
1.09 (0.73, 1.61)	Rivaroxaban (20 mg or 15 mg QD)		
0.64 (0.41, 0.98)	0.59 (0.38, 0.9)	Dabigatran (150 mg BID)	
0.88 (0.66, 1.17)	0.81 (0.62, 1.06)	1.38 (1, 1.91)	Warfarin (INR: 2-3)

BID: twice a day, QD: once a day.

Legend: Each box represents the estimated hazard ratio and 95% credible interval for the direct and indirect comparisons between two drugs: the drug at the top of the column compared to the drug at the right of the row. Estimates in bold signify that the 95% credible interval does not contain 1.0.

Table 3.4. Discontinuations of DOACs versus Warfarin

	All discontinuations	Discontinuation due to AEs
ARISTOTLE	Apixaban: 21.4%* Warfarin: 23.4%	Apixaban: 7.6% Warfarin: 8.4%
ROCKET AF	Rivaroxaban: 23.7%* Warfarin: 22.2%	Rivaroxaban: 8.3% Warfarin: 7%
RE-LY	Dabigatran: 17%* Warfarin: 12%	Dabigatran: 6.2% Warfarin: 3.3%

AEs: adverse events, AF: atrial fibrillation

* Difference between the groups met statistical significance, $p < 0.05$.

Table 3.5. Network Meta-Analysis Results for Major Bleeding.

Apixaban (5 mg or 2.5 mg BID)			
0.66 (0.54, 0.81)	Rivaroxaban (20 mg or 15 mg QD)		
0.74 (0.61, 0.91)	1.12 (0.92, 1.37)	Dabigatran (150 mg BID)	
0.69 (0.6, 0.8)	1.04 (0.9, 1.2)	0.93 (0.81, 1.07)	Warfarin (INR: 2-3)

BID: twice a day, QD: once a day.

Legend: Each box represents the estimated hazard ratio and 95% credible interval for the direct and indirect comparisons between two drugs: the drug at the top of the column compared to the drug at the right of the row. Estimates in bold signify that the 95% credible interval does not contain 1.0.

Figure 3.1. ICER Evidence Rating Matrix

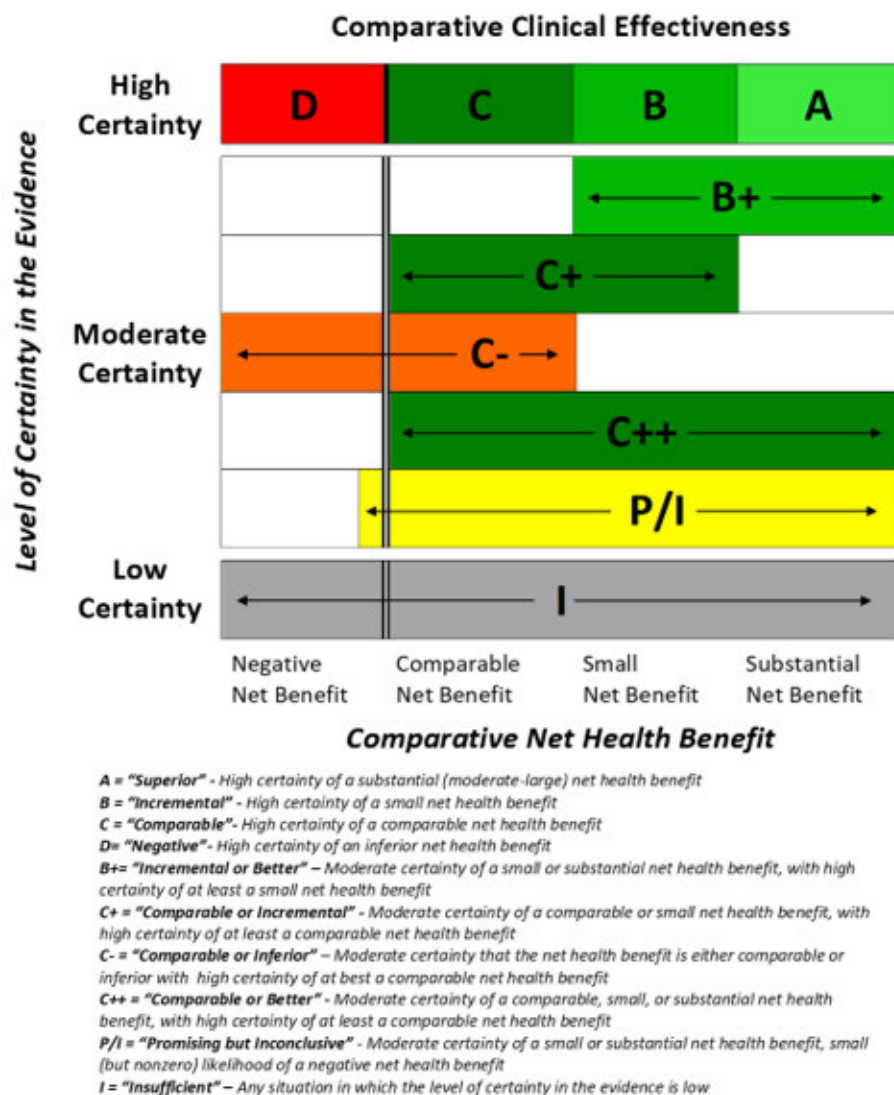


Table 3.6 Evidence Ratings

Treatment	Comparator	Evidence Rating
Apixaban	Warfarin	B
Apixaban	Dabigatran	C+
Rivaroxaban	Warfarin	B
Rivaroxaban	Dabigatran	C

Table 3.7. Lifetime Health Outcomes and Annualized Average Non-Intervention Health Care Sector Costs by Treatment Strategy

Treatment	Strokes*	MIIs	Major Bleeds**	Life Years (Discounted)	evLYs (Discounted)	Annualized non-intervention health care sector costs† (Discounted)
Apixaban	0.184	0.148	0.170	7.82	6.15	\$40,600
Rivaroxaban	0.184	0.136	0.269	7.80	6.14	\$40,700
Dabigatran	0.155	0.237	0.253	7.80	6.14	\$40,800
Warfarin	0.236	0.167	0.227	7.74	5.99	\$41,200

evLYs: equal-value life years, LY: Life year, MI: myocardial infarction

*Includes ischemic and hemorrhagic strokes

**Includes major gastrointestinal bleeds, intracranial hemorrhages, and non- gastrointestinal extracranial hemorrhages.

†Inclusive of acute event and chronic condition costs estimated over the lifetime of the model and displayed as an annualized average for each treatment strategy (excludes intervention costs).

Table 3.8. Incremental Lifetime Results for Apixaban and Rivaroxaban versus Warfarin and Dabigatran

Treatment	Incremental Lifetime Outcomes					
	Strokes*	MIIs	Major Bleeds**	Life Years (Discounted)	evLYs (Discounted)	Non-intervention health care sector costs† (Discounted)
Apixaban vs. Warfarin	-0.052	-0.019	-0.057	0.08	0.16	-\$1,800
Apixaban vs. Dabigatran	0.028	-0.089	-0.083	0.01	0.02	-\$1,100
Rivaroxaban vs. Warfarin	-0.052	-0.032	0.042	0.06	0.14	-\$1,300
Rivaroxaban vs. Dabigatran	0.028	-0.101	0.016	-0.005	-0.001	-\$600

evLYs: equal-value life years, LY: Life year, MI: myocardial infarction

Note: Negative LYs and evLYs represent life years lost with rivaroxaban vs. comparators; negative incremental strokes, Mis, and major bleeds represent events averted with rivaroxaban vs. comparators; negative costs represent cost savings for rivaroxaban vs. comparators.

*Includes ischemic and hemorrhagic strokes

**Includes major gastrointestinal bleeds, intracranial hemorrhages, and non- gastrointestinal extracranial hemorrhages.

†Inclusive of acute event and chronic condition costs (excludes intervention costs).

Table 3.9. Maximum Annualized Price Premium for Apixaban and Rivaroxaban Above Warfarin and Dabigatran Pricing to Achieve a Range of Cost-Effectiveness Price Premium Thresholds

	\$50,000/evLY	\$100,000/evLY	\$150,000/evLY	\$200,000/evLY
Apixaban vs. Warfarin	\$1,260	\$2,290	\$3,320	\$4,350
Apixaban vs. Dabigatran	\$240	\$340	\$430	\$530
Rivaroxaban vs. Warfarin	\$1,110	\$2,050	\$2,980	\$3,920
Rivaroxaban vs. Dabigatran	No price premium*	No price premium*	No price premium*	No price premium*

evLYs: equal-value life years

Note: Annualized price premiums are rounded to the nearest \$10.

*Rivaroxaban resulted in fewer evLYs gained relative to dabigatran.

Table 4.1. Overview of ESRD Studies

	Arms	Arm size	Study Duration	Baseline Characteristics					
				Age, mean (SD)	% Male	% White	CHADS ₂ , mean (SD)	CHA ₂ DS ₂ -VASc, mean (SD)	HAS-BLED, mean (SD)
Valkyrie	Rivaroxaban α	46	1.88 years*	79.9 (74.4-83.9) \ddagger	76.1	NR	NR	4.7 (1.4)	4.7 (1.4)
	Warfarin \ddagger	44		80.3 (71.5-84.3) \ddagger	56.8	NR	NR	4.8 (1.5)	4.8 (1.5)
RENAL-AF	Apixaban $\#$	82	0.93 years* \dagger	69.0 (61.0, 76.0) \ddagger	58.5	52.4	NR	NR	NR
	Warfarin \S	72		68.0 (60.5, 72.5) \ddagger	69.4	50	NR	NR	NR

AF: atrial fibrillation, CHADS₂: congestive heart failure, hypertension, age ≥ 75 (doubled), diabetes, stroke (doubled), CHA₂DS₂-VASc: congestive heart failure, hypertension, age ≥ 75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74 and sex category (female), HAS-BLED: Hypertension, Abnormal liver/renal function, Stroke history, Bleeding history or predisposition, Labile INR, Elderly, Drug/alcohol usage, NR: not reported, SD: standard deviation, %: percent

*median

\dagger Treatment was planned for up to 15 months but the study was terminated early due to a lower recruitment rate.

\ddagger median(IQR)

\S INR 2-3 dose

$\#$ Apixaban 5mg or 2.5 twice daily

α Rivaroxaban 10 mg once daily

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Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	APIXABAN
	Q26 - Respondent Name	
	Q26 - Organization Name (if applicable)	The Mended Hearts, Inc.
	Respondent Email	
Question 27: Prescribing Information	Who is completing this form?	PAO
	Prescribing Information	No response.
	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	No response.
	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	No response.

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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	No response.
	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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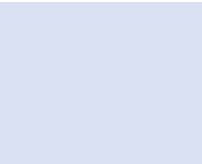
Question	Sub-Question	Response
Question 31: Patient and Caregiver Experience	Response to Question 31	
Question 32: Executive Summary	Response to Question 32	<p>Mended Hearts is the largest cardiovascular peer-to-peer patient support group in the country. We provide support and education, bring awareness to issues that those living with heart disease face and advocate to improve quality of life. Since our inception in 1951, we have assisted millions in their journey with heart disease. ..Our support network helps individuals with various cardiovascular conditions. Most often, patients find Mended Hearts because they have suffered a traumatic cardiovascular event, and they need a peer to help them navigate the physical, mental and emotional challenges of cardiovascular disease and its unfortunate consequences. ..We would like to focus our comments on a chronic condition that impacts many of our members, which is atrial fibrillation (AFib). The Centers for Disease Control estimates that by 2030, more than 12.1 million Americans will have AFib.(1) People with AFib are five times more likely to have a stroke and three times more likely to have a heart attack.(2) Apixaban is an anticoagulant medication used to reduce the risk of stroke and blood clots in patients with AFib. It works by inhibiting a specific clotting factor in the blood called factor Xa. Apixaban has been shown to be effective in preventing strokes and systemic embolism in patients with atrial fibrillation. Apixaban addresses an unmet medical need to a significant extent. The research studies indicate that apixaban effectively reduces the risk of stroke or systemic embolism in patients with atrial fibrillation.(3) ..Mended Hearts serves thousands of our nation's seniors, and we were relieved to see that the Inflation Reduction Act capped out-of-pocket spending for Medicare beneficiaries and smoothed out deductibles so seniors can pay their bills over the course of the year. Our members, however, do face numerous access challenges. Many cardiovascular patients suffer from a number of comorbid conditions and are therefore managing conditions with multiple medications. Prior authorization hurdles, non-medical switching and step therapy protocols can make "being a patient" a full-time job. We hope that CMS negotiations will ensure that patients like our members are protected from burdensome utilization management, and that they actually see the benefit of these new prices at the pharmacy counter. .. We are also concerned that the initial round of drugs had five drugs that impact our patients. We understand that the formula used to choose the drugs focuses on high volume disease states. When negotiating, we urge CMS to consider the potential for the outcome to disincentivize innovation in the cardiovascular space which would be detrimental to our members...We believe that including the patient voice in policy conversations is of the utmost importance, and we work to ensure that our patient advocates have opportunities to interface with their elected representatives and those that administer agencies like the Centers for Medicare and Medicaid Services (CMS). We are grateful that CMS has provided an opportunity to comment on the Drug Price Negotiation Program. ..1. https://www.cdc.gov/heartdisease/atrial_fibrillation.htm .2.</p>

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Question	Sub-Question
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Response
https://mendedhearts.org/wp-content/uploads/2017/03/Managing-AFib-Fact-Sheet-FINAL-10-26-15.pdf .3. https://www.nejm.org/doi/full/10.1056/nejmoa1107039

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Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	APIXABAN
	Q26 - Respondent Name	
	Q26 - Organization Name (if applicable)	Partnership to Advance Cardiovascular Health (PACH)
	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	
	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	<p>The Partnership to Advance Cardiovascular Health (PACH) is a nonprofit advocacy coalition of stakeholder groups that represent cardiovascular patients, patient advocates, health care providers, and medical researchers. On behalf of its members, PACH advocates for patient access to FDA-approved therapies and promotes innovation in cardiovascular healthcare for the millions of Americans at high risk for heart disease. ..Cardiovascular medicine has benefited from many years of breakthrough research, which has led to highly effective treatments that have enabled seniors to live longer, healthier lives. However, heart disease continues to be the #1 killer in America, accounting for 1 in every 5 deaths in 2021. ..Cardiovascular disease disproportionately impacts vulnerable communities, including minorities, aging populations, rural communities, and those with lower socioeconomic status. For example, black men have a 70% higher risk of heart failure (HF), and black women have a 50% higher risk than their white counterparts. Yet racial and ethnic minorities receive less than 40% of total annual advanced HF therapies – and women receive less than a quarter. Similarly, atrial fibrillation (AF) is the most common cardiac arrhythmia in the United States, and patients with AF are five times more likely to experience an ischemic stroke. Medicare claims studies have shown that Black and Hispanic patients over 65 with AF had a higher unadjusted risk of death and stroke. ..Apixaban is used to treat and prevent blood clots, including deep vein thrombosis (DVT) and pulmonary embolism. Apixaban also prevents stroke for patients with nonvalvular atrial fibrillation. In addition to assisting those with cardiovascular disease, apixaban is often used during hip and knee replacement surgeries to prevent clotting. Compared to its alternative – warfarin – apixaban is far safer and more effective. A 2021 study indicates that, compared to warfarin, apixaban is associated with a reduced risk of stroke and systemic embolism. Both standard and reduced doses of apixaban showed lower risk of major bleeding than those with warfarin.¹ Because of apixaban and other direct oral anticoagulants, fewer people in America experience strokes, deep vein thrombosis and pulmonary embolism. Its value to patients and the healthcare system is well established. ..As an organization that represents cardiovascular patients and prescribers, we believe it is notable that cardiovascular agents are disproportionately represented in price negotiations. Our goal is to ensure that the 42% of Medicare beneficiaries who have been diagnosed with a heart condition can still receive current and future medications they need to prevent heart attacks and strokes. While we steadfastly agree that lowering the cost of medications for our vulnerable seniors is a priority, we remain concerned that the Inflation Reduction Act Medicare Drug Price Negotiation Program could negatively impact innovation and access to life-saving medications. ..We recognize IRA has implications for future research and development as well as access to current medicines. We urge CMS to take steps now to ensure the drug negotiation program is patient-centric and equitable for the millions of Medicare beneficiaries diagnosed with cardiovascular disease</p>
Question 32: Executive Summary	Response to Question 32	

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Question	Sub-Question
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	Response
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	<p>today and in the long run. If PACH or our members can be a resource to CMS, please do not hesitate to contact us. Considering that the IRA will disproportionately impact cardiovascular patients, we would welcome meeting with CMS to discuss our concerns and offer insights from the community. . . .1. Fu CM, Li LC, Lee YT, Wang SW, Hsu CN. Apixaban vs. Warfarin in Atrial Fibrillation Patients With Chronic Kidney Disease. Front Cardiovasc Med. 2021 Oct 18;8:752468. doi: 10.3389/fcvm.2021.752468. PMID: 34733897; PMCID: PMC8558356.</p>
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Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	APIXABAN
	Q26 - Respondent Name	
	Q26 - Organization Name (if applicable)	Patients For Affordable Drugs
	Respondent Email	
	Who is completing this form?	PAT
Question 27: Prescribing Information	Prescribing Information	I take this drug twice daily to prevent blood clots due to Atrial Fibrillation and risk of blood clots from cancer drugs I am prescribed. I have also had a blood clot in the past. Alternatives include Xarelto, which is an inferior alternative with higher rates of clots, stroke and death.
	Evidence Submitted include a cost-effectiveness measure?	N
	What type of Evidence is shown?	
Question 28: Therapeutic Impact and Comparative Effectiveness	Therapeutic Impact and Comparative Effectiveness	See above for bullet one..Eliquis is superior to earlier anti-coagulants such as Coumadin..My drug plan offered me \$799 out of pocket for a 90-day supply of Eliquis, and \$170 oop for a 90-day supply of Xarelto..I bought apixiban from a Canadian pharmacy for \$260 oop a 90 day supply..Eliquis list price is about \$6700 in the US and less than \$1700 in Canada.
	Hyperlink to Table/Charts/Graphs - Additional Materials for Question 28	
	Evidence Submitted include a cost-effectiveness measure?	
	What type of Evidence is shown?	

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Question	Sub-Question	Response
Question 29: Comparative Effectiveness on Specific Populations	Response to Question 29	I don't know the answers to these questions.
	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	No. There are a range of options, but Eliquis is the best in my opinion as a patient.
	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

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Question	Sub-Question	Response
	What type of Evidence is shown?	
Question 31: Patient and Caregiver Experience	Response to Question 31	I have been taking apixiban since April, 2023. It has worked in that I have not experienced a blood clot. It has not affected my quality of life.
Question 32: Executive Summary	Response to Question 32	

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Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	APIXABAN
	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?	
Question 28: Therapeutic Impact and Comparative Effectiveness	What type of Evidence is shown?	
	Therapeutic Impact and Comparative Effectiveness	<p>The Pharmaceutical Care Management Association (PCMA) appreciates the opportunity to submit comments regarding the therapeutic alternatives for Apixaban. Our members help administer the Part D prescription drug benefit on behalf of many Part D plan sponsors, and a central component of that function is the identification of therapeutic alternatives to develop comprehensive prescription drug formularies consistent with applicable statutory, regulatory, and clinical requirements, including ensuring formularies are not discriminatory...In general, while we understand that CMS cannot disclose the specifics of their negotiations with manufacturers of selected drugs, we believe the public is best served by CMS disclosing as much about this process as possible, and otherwise aligning its methodology for selecting therapeutic alternatives with how Part D plans select therapeutic alternatives. Our comments focus on emphasizing the differences between identifying therapeutic alternatives for purposes of the Medicare Drug Price Negotiation Program, and the role that the identification of therapeutic alternatives plays under the Medicare Part D program's formulary standards and enrollee communication requirements. PCMA has three main points:...</p> <p>1. As a general principle, CMS should identify therapeutic alternatives under the Medicare Drug Price Negotiation Program consistent with the guardrails that apply to Part D plan sponsors when identifying therapeutic alternatives for the Part D program.</p> <p>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...</p> <p>3. CMS</p>

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Question	Sub-Question
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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
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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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Question	Sub-Question
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Question	Sub-Question	Response
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		<p>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</p>
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Question	Sub-Question	Response
		provides plans with significant flexibility in the selection of those therapeutic alternatives. As such, CMS should explicitly clarify that the information on therapeutic alternatives that Part D plans choose to communicate to enrollees in required enrollee communications to beneficiaries and other regulatory requirements is not affected by CMS's selection of therapeutic alternatives for purposes of the Medicare Drug Price Negotiation Program.
	Hyperlink to Table/Charts/Graphs - Additional Materials for Question 28	
	Evidence Submitted include a cost-effectiveness measure?	
Question 29: Comparative Effectiveness on Specific Populations	What type of Evidence is shown?	
	Response to Question 29	
	Hyperlink to Citation - Additional Materials for Question 29	
	Hyperlink to Table/Charts/Graphs - Additional Materials for Question 29	
	Evidence Submitted include a cost-effectiveness measure?	
	What type of Evidence is shown?	

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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 Apixaban. 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.

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Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	APIXABAN
	Q26 - Respondent Name	
	Q26 - Organization Name (if applicable)	Right Care Initiative, UC Berkeley
	Respondent Email	
	Who is completing this form?	HCW
Question 27: Prescribing Information	Prescribing Information	Stroke and Systemic Embolism Prevention in Atrial Fibrillation, VTE and Pulmonary Embolism Treatment, BTE prevention, VTE prevention following Knee and Hip Surgery.
	Evidence Submitted include a cost-effectiveness measure?	Y
	What type of Evidence is shown?	N
Question 28: Therapeutic Impact and Comparative Effectiveness	Therapeutic Impact and Comparative Effectiveness	<p>CMS: Anticoagulants for Medicare ...Apixaban has been shown to be as effective or better and significantly safer than it's alternatives in multiple trials and meta-analyses...Buckley (Benjamin J. R. Buckley, Deirdre A. Lane, Peter Calvert, Juqian Zhang, David Gent, C. Daniel Mullins, Paul Dorian, Shun Kohsaka, Stefan H. Hohnloser, Gregory Lip: Effectiveness and Safety of Apixaban in over 3.9 Million People with Atrial Fibrillation: A Systematic Review and Meta-Analysis; J. Clinical Medicine 2022 Jul: 11(13):3788) compared apixaban with alternative anticoagulants in 3.9 million AF patients. For stroke/systemic embolus apixaban showed reduced relative risk ratios of 0.77(.64-.93) vs comparator, 0.84(.74-.95) vs dabigatran, and 0.90(.78-1.03) vs rivaroxaban. For mortality apixaban showed a risk ratio of 0.72(.50-1.02) vs VKA, 1.00(.82-1.22) vs dabigatran, and 0.83(.71-.96) vs rivaroxaban. For major bleeds apixaban showed a significant risk reductions for apixaban of 0.58(.52-.65) vs VKA, 0.79(.70-.88) vs Dabigatran, and 0.61(.53-.72) vs rivaroxaban.....Ray (Ray, Chung, Stein et al; Association of Rivaroxaban vs Apixaban with Major Ischemic or Hemorrhagic Events in Patients with Atrial Fibrillation; JAMA. 2021;326(23a02395-2404)) compared apixaban versus rivaroxaban using propensity score methods in 581,451 patients with atrial fibrillation for US Medicare beneficiaries >65 years. Major ischemic and bleeding events were compared for rivaroxaban vs apixaban: major ischemic and hemorrhagic-16.1 vs 13.4/1000 pt-years; ischemic-8.6 vs 7.6; hemorrhagic-7.5 vs 5.9; and non-fatal bleeding-39.7 vs 45.4. This represents a total reduction of 26.4 (71.8-45.4)/1000 events in the apixaban patients and a NNT of 37.87. Thus using apixaban could prevent over 12,000 events/year in this cohort. The projected cost savings in reducing</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>excess Medicare hospitalization costs would total \$164 million/year(average cost/hospitalization \$13,093)....Friedman (Efficacy and Safety of Rivaroxaban Versus Apixaban in Patients with Venous Thromboembolism: A Systematic Review and Meta-Analysis of Observational Studies; Danielle Fredman, Rotem McNeil, Ofir Eldar, Avi Leader, Anat Gafter-Gvili, Tomer Avni; Blood (2022) 140 (Supplement 1): 5664-5665) examined 9 observational studies in a meta-analysis, assessing 24,156 patients for apixaban and 38,847 for rivaroxaban showing a trend towards lower risk of rVTE with apixaban compared to rivaroxaban (RR 0.77, 95% CI 0.57-1.04). The analysis of the primary safety outcome showed a significantly lower risk of major bleeding with apixaban compared to rivaroxaban (RR 0.68, 95% CI 0.61-0.76). Apixaban was associated with significantly decreased risk of net clinical harm, clinically relevant non-major bleeding (CRNMB) and any bleeding, compared to rivaroxaban (RR 0.75, 95% CI 0.61-0.92, I²=50%; RR 0.58, 95% CI 0.50-0.67, I²=7%; RR 0.64, 95% CI 0.59-0.70, I²= 0%, respectively)...In summary apixaban is as effective or better in reducing Stroke and Systemic emboli in Atrial Fibrillation and recurrent VTE in VTE patients. For patient safety, apixaban significantly reduces major bleeding complications by almost half. In addition to saving morbidity this can also reduce hospital costs in our Medicare population.</p>
Question 29: Comparative Effectiveness on Specific Populations	Response to Question 29	<p>N</p> <p>CMS: Anticoagulants for Medicare ...Apixaban has been shown to be as effective or better and significantly safer than it's alternatives in multiple trials and meta-analyses...Buckley (Benjamin J. R. Buckley, Deirdre A. Lane, Peter Calvert,Juqian Zhang, David Gent, C. Daniel Mullins, Paul Dorian, Shun Kohsaka, Stefan H. Hohnloser, Gregory Lip: Effectiveness and Safety of Apixaban in over 3.9 Million People with Atrial Fibrillation: A Systematic Review and Meta-Analysis; J. Clinical Medicine 2022 Jul: 11(13):3788) compared apixaban with alternative anticoagulants in 3.9 million AF patients. For stroke/systemic embolus apixaban showed reduced relative risk ratios of 0.77(.64-.93) vs comparator, 0.84(.74-.95) vs dabigatran, and 0.90(.78-1.03) vs rivaroxaban. For mortality apixaban showed a risk ratio of 0.72(.50-1.02) vs VKA, 1.00(.82-1.22) vs dabigatran, and 0.83(.71-.96) vs rivaroxaban. For major bleeds apixaban showed a significant risk reductions for apixaban of 0.58(.52-.65) vs VKA, 0.79(.70-.88) vs Dabigatran, and 0.61(.53-.72) vs rivaroxaban.....Ray (Ray, Chung, Stein et al; Association of Rivaroxaban vs Apixaban with Major Ischemic or Hemorrhagic Events in Patients with Atrial</p>

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Question	Sub-Question
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Response

Fibrillation; JAMA. 2021;326(23a02395-2404)) compared apixaban versus rivaroxaban using propensity score methods in 581,451 patients with atrial fibrillation for US Medicare beneficiaries >65 years. Major ischemic and bleeding events were compared for rivaroxaban vs apixaban: major ischemic and hemorrhagic-16.1 vs 13.4/1000 pt-years; ischemic-8.6 vs 7.6; hemorrhagic-7.5 vs 5.9; and non-fatal bleeding-39.7 vs 45.4. This represents a total reduction of 26.4 (71.8-45.4)/1000 events in the apixaban patients and a NNT of 37.87. Thus using apixaban could prevent over 12,000 events/year in this cohort. The projected cost savings in reducing excess Medicare hospitalization costs would total \$164 million/year(average cost/hospitalization \$13,093)....Friedman (Efficacy and Safety of Rivaroxaban Versus Apixaban in Patients with Venous Thromboembolism: A Systematic Review and Meta-Analysis of Observational Studies; Danielle Fredman, Rotem McNeil, Ofir Eldar, Avi Leader, Anat Gafter-Gvili, Tomer Avni; Blood (2022) 140 (Supplement 1): 5664-5665) examined 9 observational studies in a meta-analysis, assessing 24,156 patients for apixaban and 38,847 for rivaroxaban showing a trend towards lower risk of rVTE with apixaban compared to rivaroxaban (RR 0.77, 95% CI 0.57-1.04). The analysis of the primary safety outcome showed a significantly lower risk of major bleeding with apixaban compared to rivaroxaban (RR 0.68, 95% CI 0.61-0.76). Apixaban was associated with significantly decreased risk of net clinical harm, clinically relevant non-major bleeding (CRNMB) and any bleeding, compared to rivaroxaban (RR 0.75, 95% CI 0.61-0.92, I2=50%; RR 0.58, 95% CI 0.50-0.67, I2=7%; RR 0.64, 95% CI 0.59-0.70, I2= 0%, respectively)...In summary apixaban is as effective or better in reducing Stroke and Systemic emboli in Atrial Fibrillation and recurrent VTE in VTE patients. For patient safety, apixaban significantly reduces major bleeding complications by almost half. In addition to saving morbidity this can also reduce hospital costs in our Medicare population.

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?

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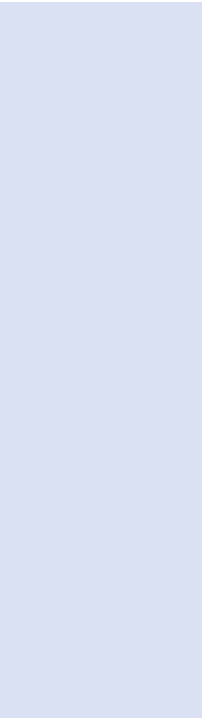
Question	Sub-Question	Response
	What type of Evidence is shown?	
Question 30: Addressing Unmet Medical Needs	Response to Question 30	No
	Hyperlink to Citation - Additional Materials for Question 30	
	Hyperlink to Table/Charts/Graphs - Additional Materials for Question 30	
	Evidence Submitted include a cost-effectiveness measure?	Y
	What type of Evidence is shown?	N
Question 31: Patient and Caregiver Experience	Response to Question 31	
Question 32: Executive Summary	Response to Question 32	<p>CMS: Anticoagulants for Medicare ...Apixaban has been shown to be as effective or better and significantly safer than it's alternatives in multiple trials and meta-analyses...Buckley (Benjamin J. R. Buckley, Deirdre A. Lane, Peter Calvert, Juqian Zhang, David Gent, C. Daniel Mullins, Paul Dorian, Shun Kohsaka, Stefan H. Hohnloser, Gregory Lip: Effectiveness and Safety of Apixaban in over 3.9 Million People with Atrial Fibrillation: A Systematic Review and Meta-Analysis; J. Clinical Medicine 2022 Jul: 11(13):3788) compared apixaban with alternative anticoagulants in 3.9 million AF patients. For stroke/systemic embolus apixaban showed reduced relative risk ratios of 0.77(.64-.93) vs comparator, 0.84(.74-.95) vs dabigatran, and 0.90(.78-1.03) vs rivaroxaban. For mortality apixaban showed a risk ratio of 0.72(.50-1.02) vs VKA, 1.00(.82-1.22) vs dabigatran, and 0.83(.71-.96) vs rivaroxaban. For major bleeds apixaban showed a significant risk reductions for apixaban of 0.58(.52-.65) vs VKA, 0.79(.70-.88) vs Dabigatran, and 0.61(.53-.72) vs rivaroxaban.....Ray (Ray, Chung, Stein et al; Association of Rivaroxaban vs Apixaban with Major Ischemic or Hemorrhagic Events in Patients with Atrial</p>

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Question	Sub-Question
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Response

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Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	APIXABAN
	Q26 - Respondent Name	
	Q26 - Organization Name (if applicable)	Rutgers University and The Professional Society for Health Economics and Outcomes Research (ISPOR) [Dr. Laura Pizzi and Dr. Richard Willke]
	Respondent Email	
Question 27: Prescribing Information	Who is completing this form?	NAR
	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	This abstract information is collected from the ISPOR Presentations Database. The database includes scientific abstracts on apixaban presented at ISPOR conferences, along with links to research poster PDFs or PowerPoint research slide decks, where available. "This searchable resource includes more than 60,000 citable research abstracts of podium and poster presentations from ISPOR conferences that were published in Value in Health since 1998 in addition to recent non-citable session presentations from the Society's conferences." Included abstracts may not reflect final results, and the posters have not undergone scientific review.
	Hyperlink to Table/Charts/Graphs - Additional Materials for Question 28	
	Evidence Submitted include a cost-effectiveness measure?	
	What type of Evidence is shown?	

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

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Question	Sub-Question	Response
	What type of Evidence is shown?	
Question 31: Patient and Caregiver Experience	Response to Question 31	
Question 32: Executive Summary	Response to Question 32	

