

Redacted Data Submitted by the Primary Manufacturer and Other Interested Parties for NovoLog/Fiasp

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: Novo Nordisk Inc.

Drug: Novolog/Fiasp (InsulinAspart)

Background: For the first year of the Medicare Drug Price Negotiation Program (“the Negotiation Program”), CMS selected 10 Part D high expenditure, single source drugs for negotiation. Section 1194(e) of the Act requires Centers for Medicare & Medicaid Services (CMS) to consider two sets of factors as the basis for determining the offer and counteroffer throughout the negotiation process: (1) certain data that must be submitted by the manufacturer of each drug selected for negotiation and (2) evidence about alternative treatments, as available, with respect to each selected drug and therapeutic alternative(s) for each selected drug. After entering into an agreement under the Negotiation Program with CMS and in accordance with section 1193(a)(4) of the Act, the Primary Manufacturer of each selected drug submitted to CMS the following information with respect to a selected drug: information that CMS required to carry out negotiation, including but not limited to the factors listed in section 1194(e)(1) of the Act. For IPAY 2026, the Primary Manufacturer of each selected drug were tasked to provide the following data factors for each of its selected drug(s), which were specifically:

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

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

Disclaimers: With the exclusion of publicly available data, all manufacturer submitted data is considered proprietary and confidential. The data contained in this document are solely those of the authors and do not necessarily reflect the views or policies of CMS. The authors assume responsibility for the accuracy and completeness of the information contained in this document.

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

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

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

Explanations:

Explanation of Basic Pre-Clinical Research Costs

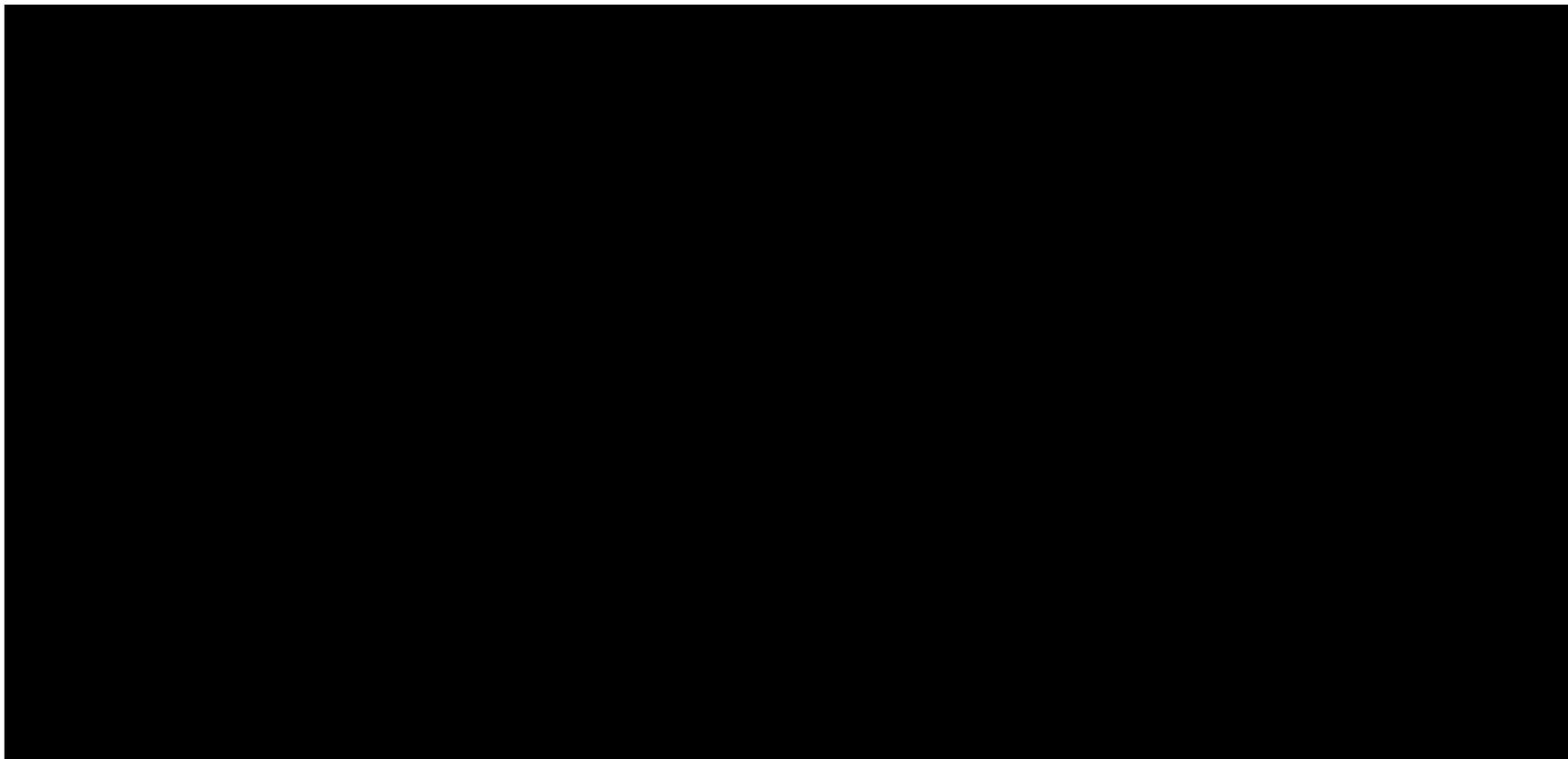
- This response contains trade secret and confidential commercial and financial information that Novo Nordisk customarily and actually treats as private. Disclosure of this information would result in harm to Novo Nordisk’s business interests, including because disclosure of any individual piece(s) of information could result in public identification of confidential materials. Novo Nordisk submits this

information under CMS's assurances of confidentiality (Guidance § 40.2.1 (citing id. § 40.2.2; 5 U.S.C. § 552(b)(3), (4); 18 U.S.C. § 1905)) and designates this submission as confidential and exempt from disclosure under Exemption 4 of the FOIA (45 C.F.R. 5.41). As such, predislosure notification is required (45 C.F.R. 5.42). Novo Nordisk's future disclosure of any piece of the information contained herein and designated as confidential does not alter the status of the remaining information as exempt from disclosure or otherwise waive or forfeit Novo Nordisk's rights to confidential treatment and predislosure notification.

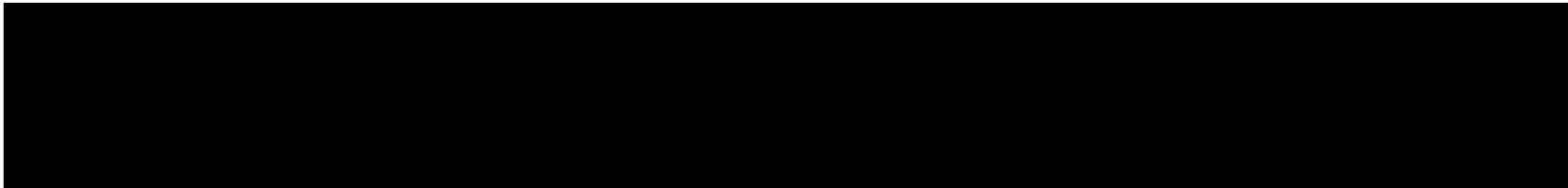
- By completing the data submission, Novo Nordisk preserves and does not waive or forfeit any of its rights, arguments, or objections relating either to the constitutionality of the Inflation Reduction Act or the legality of the actions taken by CMS, including how CMS intends to use this data for purposes of setting a maximum fair price. For example, Novo Nordisk strongly opposes the concept of considering whether research and development costs have been recouped for purposes of setting an MFP, as the IRA contemplates, because it is based on an inherent misunderstanding of the operations of a large and complex global pharmaceutical company like Novo Nordisk. This approach truncates the true value of the actual costs invested in, and risks associated with, bringing successful pharmaceutical products to market. CMS fails to consider lifetime, global costs that are associated with researching, developing, producing, distributing and selling prescription drugs, including related indirect costs, as well as comprehensive research and development costs associated with failures beyond those captured by CMS's overly limiting criteria. The approach fails to consider the reality of pharmaceutical product development, approval, and pricing, and creates an inaccurate impression as to whether a manufacturer has actually recouped its costs to develop and bring a product to market. Moreover, the determination of purported net profit as per the guidelines in the ICR does not take into consideration several key cost components that are critical for the operations of a global organization. For example, the ICR does not account for the effective tax rate that Novo Nordisk pays to various tax authorities around the world, or capital expenditures and other investments to expand manufacturing and fill-finish capacity, or funding of organic growth opportunities and re-investments through acquisitions, among other key costs. Looking at purported "revenue" and "profits" of a single product/compound in a silo does not provide a holistic view of the net profits of a global organization and the various other necessary risks and sunk costs incurred.
- All costs reported in response to this question are direct research costs specifically attributable to the pre-clinical research project at issue. Within Novo Nordisk's financial recording and reporting system, direct costs encompass both external costs, meaning Novo Nordisk expenditures directly associated with specific projects or trials conducted by external parties, and internal Line of Business (LoB) costs, meaning those expenditures associated with the respective in-house activities conducted related to a product.

The following describes the method for identifying external and internal project costs related to the selected products:

- External project costs for purposes of pre-clinical research included: researching and establishing screening plan, lead series identification and compound optimization, early assay development, in vitro and in vivo Absorption, Distribution, Metabolism, and Excretion (ADME) studies, toxicology studies, and documentation and delivery before IND application (e.g., compiling data, study reports, and other relevant documentation).



- When CMS references “labeled indications,” Novo Nordisk interprets that to mean the current label, including all indications included on the current label for the selected products. Novo Nordisk has included research and development costs relative to all research used to support all labeled indications of the subject products, including any indications that were obtained after initial approvals.
- [REDACTED] The day before the last IND application for an FDA-approved indication of the selected drug went into effect was June 28, 1995 for NovoLog® and January 31, 2010 for Fiasp®.





Other Assumptions:

- When calculating and reporting monetary amounts, Novo Nordisk used International Financial Reporting Standards (IFRS), as those are the company's established accounting standards.
- Novo Nordisk did not use cost of capital adjustments in this response, as the responsive projects were developed in-house and not part of any merger and acquisition.
- Novo Nordisk utilized the USDA Yearly Average Exchange conversion rates to convert DKK to USD.

Explanation of Post-IND Costs

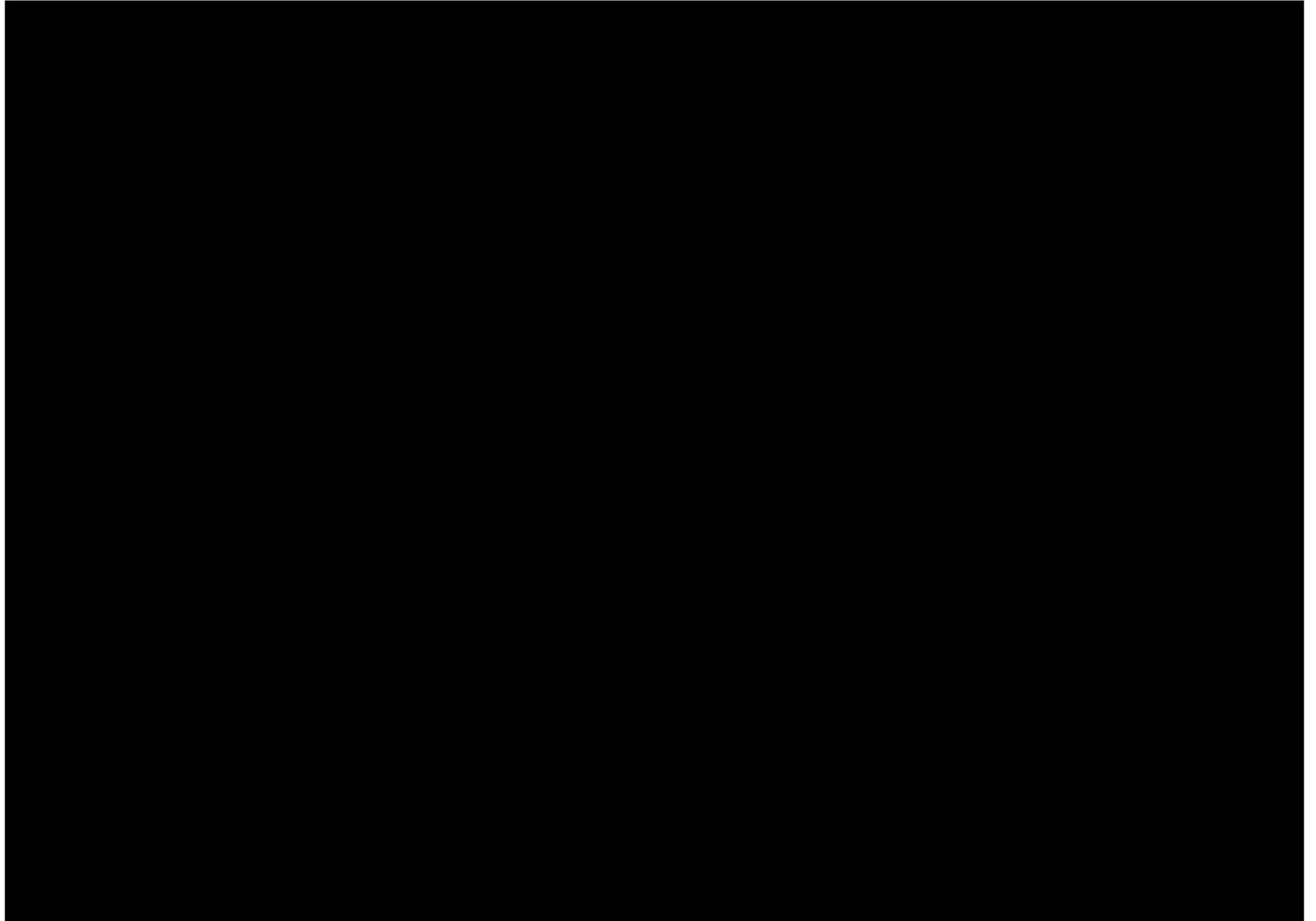
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- By completing the data submission, Novo Nordisk preserves and does not waive or forfeit any of its rights, arguments, or objections relating either to the constitutionality of the Inflation Reduction Act or the legality of the actions taken by CMS, including how CMS

intends to use this data for purposes of setting a maximum fair price. For example, Novo Nordisk strongly opposes the concept of considering whether research and development costs have been recouped for purposes of setting an MFP, as the IRA contemplates, because it is based on an inherent misunderstanding of the operations of a large and complex global pharmaceutical company like Novo Nordisk. This approach truncates the true value of the actual costs invested in bringing successful pharmaceutical products to market. CMS fails to consider lifetime, global costs that are associated with researching, developing, producing, distributing and selling prescription drugs, including related indirect costs, as well as comprehensive research and development costs associated with failures beyond those captured by CMS's overly limiting criteria. The approach fails to consider the reality of pharmaceutical product development, approval, and pricing, and creates an inaccurate impression as to whether a manufacturer has actually recouped its costs to develop and bring a product to market. Moreover, the determination of purported net profit as per the guidelines in the ICR does not take into consideration several key cost components that are critical for the operations of a global organization. For example, the ICR does not account for the effective tax rate that Novo Nordisk pays to various tax authorities around the world, or capital expenditures and other investments to expand manufacturing and fill-finish capacity, or funding of organic growth opportunities and re-investments through acquisitions, among other key costs. Looking at purported "revenue" and "profits" of a single product/compound in a silo does not provide a holistic view of the net profits of a global organization and the various other necessary risks and sunk costs incurred.

- NovoLog® and Fiasp® were each approved by FDA in an NDA (and each NDA was later deemed to be a BLA). Novo Nordisk did not receive priority review or expedited approval (e.g., accelerated approval) for either product. [REDACTED]

[REDACTED] The INDs for both products are still open, and as such, the post-IND timeframe runs through the current calendar year.

- External costs refer to expenditures directly associated with specific projects or trials conducted by external parties, such as research partners, contract research organizations (CROs), and other third-party collaborators, including clinical trial costs linked to specific projects/trials, conduct of clinical trials with subjects, exploratory clinical trials and post-marketing studies, and clinical development activities and regulatory submissions.





Other Assumptions:

- When calculating and reporting monetary amounts, Novo Nordisk used International Financial Reporting Standards (IFRS), as those are the company's established accounting standards.
- Novo Nordisk did not use cost of capital adjustments in this response, as the responsive projects were developed in-house and not part of any merger and acquisition.
- Novo Nordisk utilized the USDA Yearly Average Exchange conversion rates to convert DKK to USD.

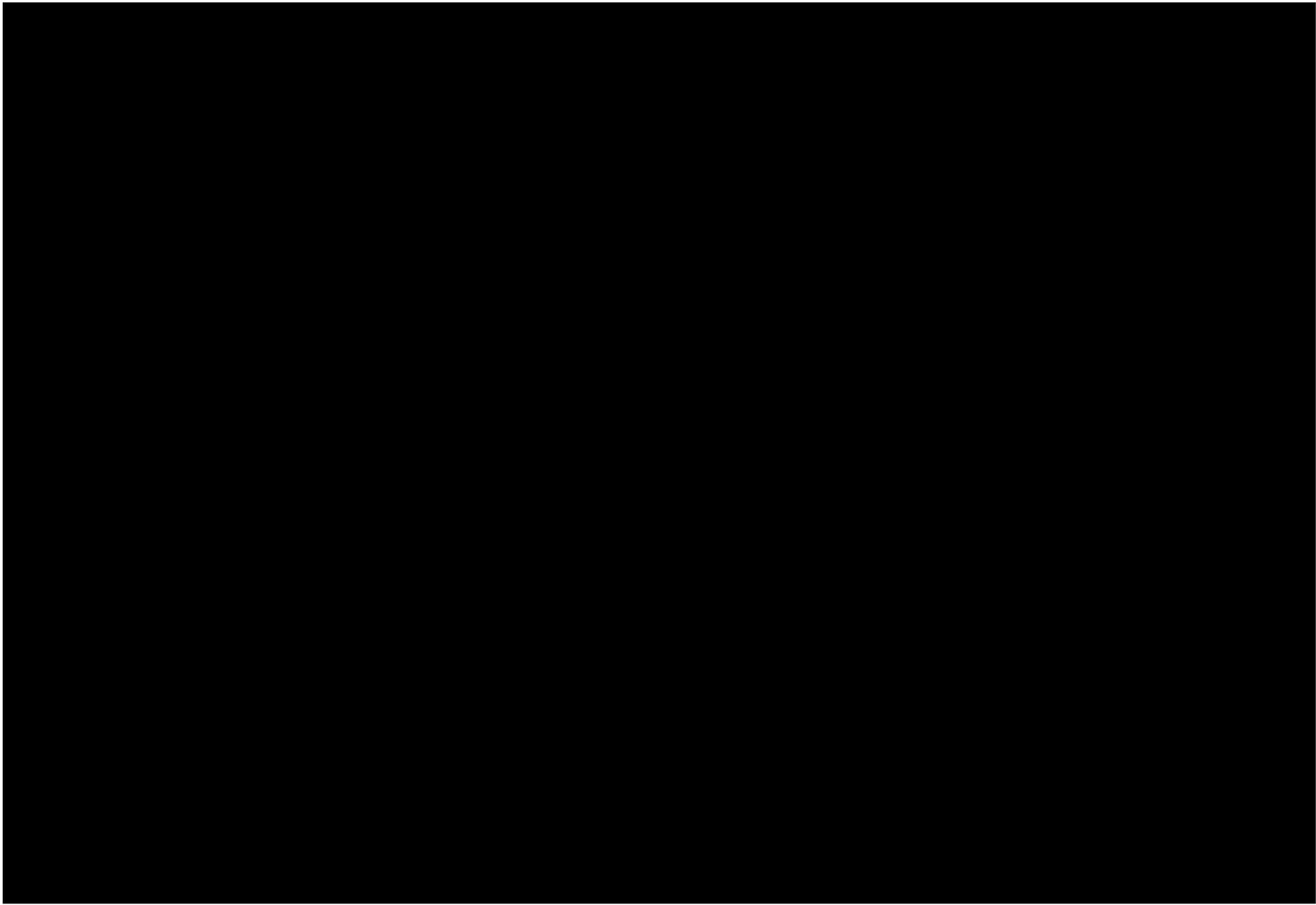
Explanation of Costs on Allowable

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information under CMS's assurances of confidentiality (Guidance § 40.2.1 (citing id. § 40.2.2; 5 U.S.C. § 552(b)(3), (4); 18 U.S.C. § 1905)) and designates this submission as confidential and exempt from disclosure under Exemption 4 of the FOIA (45 C.F.R. 5.41). As such, predisdisclosure notification is required (45 C.F.R. 5.42). Novo Nordisk's future disclosure of any piece of the information contained herein and designated as confidential does not alter the status of the remaining information as exempt from disclosure or otherwise waive or forfeit Novo Nordisk's rights to confidential treatment and predisdisclosure notification.

- By completing the data submission, Novo Nordisk preserves and does not waive or forfeit any of its rights, arguments, or objections relating either to the constitutionality of the Inflation Reduction Act or the legality of the actions taken by CMS, including how CMS intends to use this data for purposes of setting a maximum fair price. For example, Novo Nordisk strongly opposes the concept of considering whether research and development costs have been recouped for purposes of setting an MFP, as the IRA contemplates, because it is based on an inherent misunderstanding of the operations of a large and complex global pharmaceutical company like Novo Nordisk. This approach truncates the true value of the actual costs invested in bringing successful pharmaceutical products to market. CMS fails to consider lifetime, global costs that are associated with researching, developing, producing, distributing and selling prescription drugs, including related indirect costs, as well as comprehensive research and development costs associated with failures beyond those captured by CMS's overly limiting criteria. The approach fails to consider the reality of pharmaceutical product development, approval, and pricing, and creates an inaccurate impression as to whether a manufacturer has actually recouped its costs to develop and bring a product to market. Moreover, the determination of purported net profit as per the guidelines in the ICR does not take into consideration several key cost components that are critical for the operations of a global organization. For example, the ICR does not account for the effective tax rate that Novo Nordisk pays to various tax authorities around the world, or capital expenditures and other investments to expand manufacturing and fill-finish capacity, or funding of organic growth opportunities and re-investments through acquisitions, among other key costs. Looking at purported "revenue" and "profits" of a single product/compound in a silo does not provide a holistic view of the net profits of a global organization and the various other necessary risks and sunk costs incurred.
- Novo Nordisk included failed or abandoned projects that can be directly attributed to failed or abandoned product(s) with the same active moiety / active ingredient or mechanism of action or drugs in the same therapeutic class as the selected drugs that did not achieve FDA approval, [REDACTED]

[REDACTED]





Other Assumptions:

- When calculating and reporting monetary amounts, Novo Nordisk used International Financial Reporting Standards (IFRS), as those are the company's established accounting standards.
- Novo Nordisk did not use cost of capital adjustments in this response, as the responsive projects were developed in-house and not part of any merger and acquisition.
- Novo Nordisk utilized the USDA Yearly Average Exchange conversion rates to convert DKK to USD.

Explanation of Costs of Other R&D

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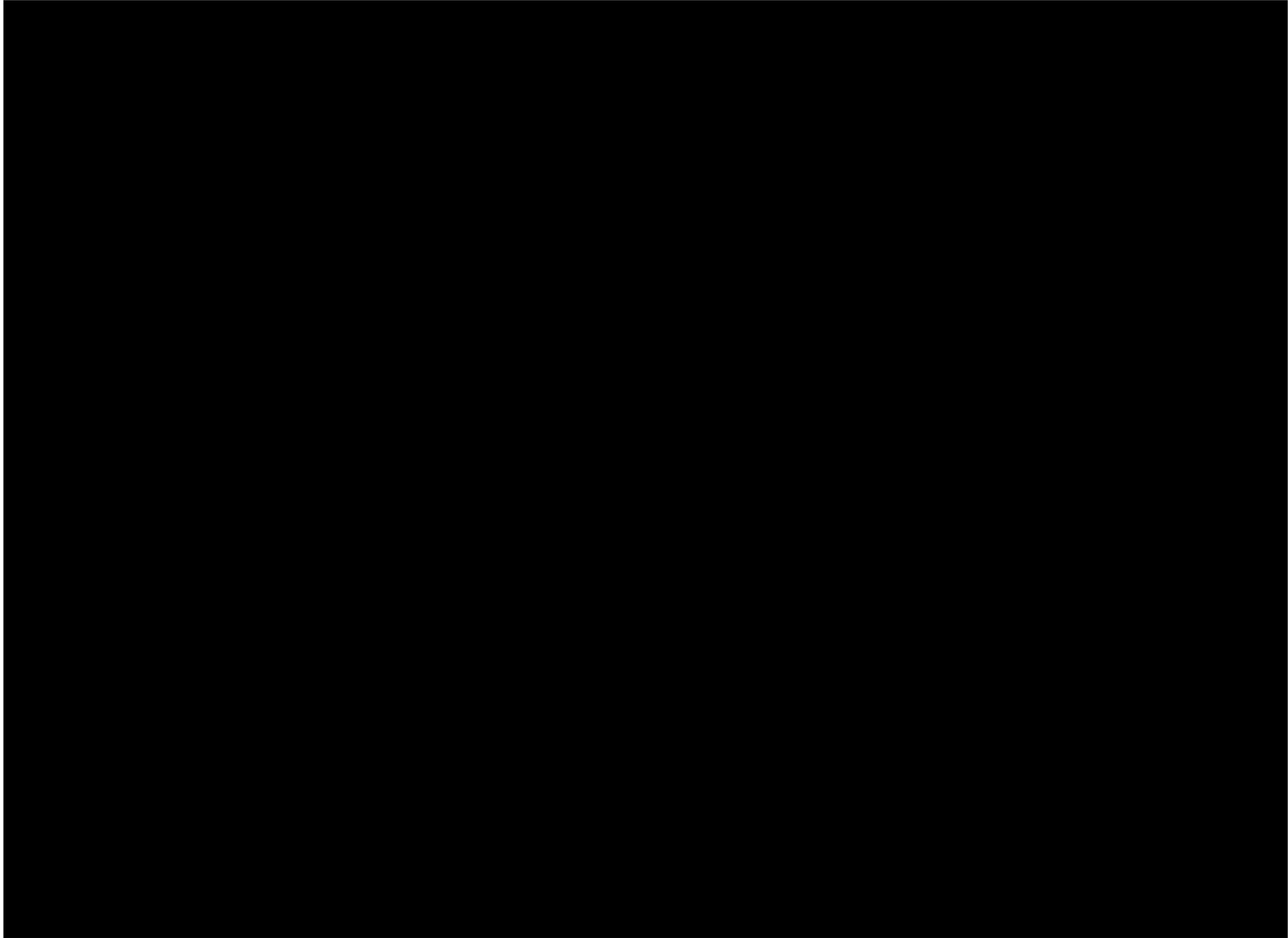
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- The scope of this response includes any research and development spend related to insulin aspart not otherwise accounted for in one of the previous responses, including non-clinical research and development costs associated with FDA approval, submission, launch activities, and life cycle management of NovoLog® and Fiasp® (excluding those costs captured in previous questions).

-

[REDACTED]

The inclusion of these related R&D costs enables Novo Nordisk to be collectively exhaustive for all relevant research and development costs in questions 2 through 5.

[REDACTED]





Other Assumptions:

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- Novo Nordisk did not use cost of capital adjustments in this response, as the responsive projects were developed in-house and not part of any merger and acquisition.
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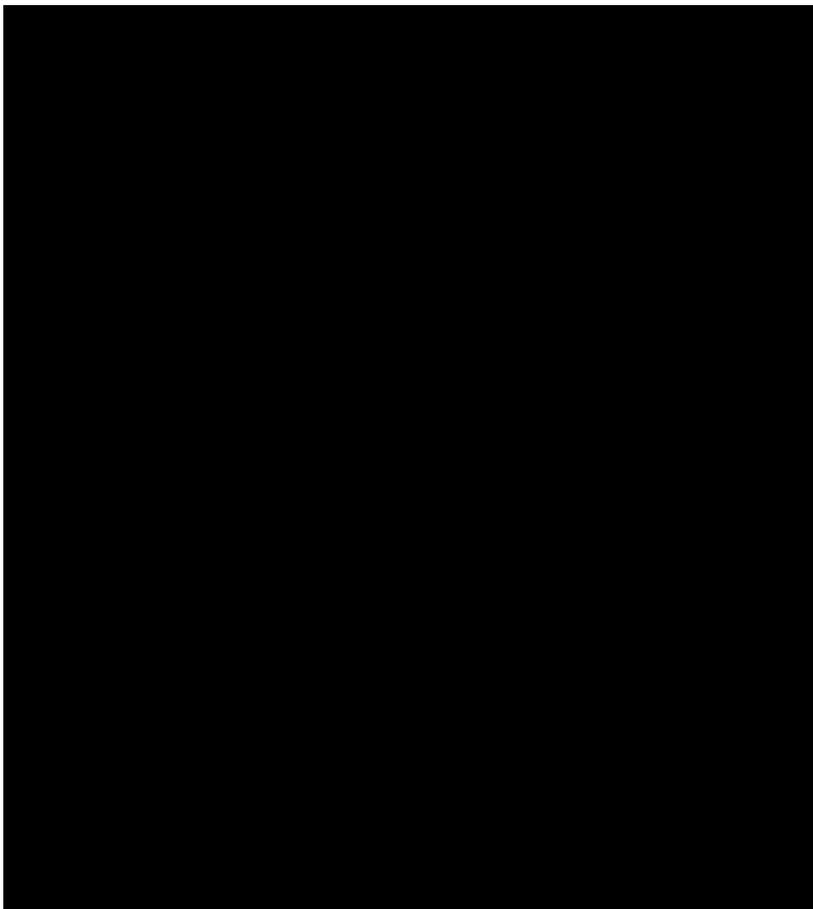
Explanation of Global

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- When calculating and reporting monetary amounts, Novo Nordisk used International Financial Reporting Standards (IFRS), as those are the company’s established accounting standards.
- NovoLog® was first sold globally in 1999, and Fiasp® was first sold globally in 2017.

- Novo Nordisk utilized the USDA Yearly Average Exchange conversion rates to convert DKK to USD.



Explanation of U.S. Lifetime Net Revenue

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- When calculating and reporting monetary amounts, Novo Nordisk used International Financial Reporting Standards (IFRS), as those are the company's established accounting standards.
- NovoLog® was first marketed in the United States in 2001. Fiasp® was first marketed in the United States in 2018.



[Redacted]

- Novo Nordisk utilized the USDA Yearly Average Exchange conversion rates to convert DKK to USD.

[Redacted]

D. Current Unit Costs of Production and Distribution

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

NDC-11	Average Per Unit Production Cost	Average Per Unit Distribution Costs	Indicate Unit Used	Total Unit Volume
00169-3204-15			ML	
00169-3201-11			ML	
00169-3205-15			ML	
73070-0100-11			ML	
73070-0102-15			ML	
73070-0103-15			ML	
00169-3303-12			ML	
00169-2101-25			ML	
00169-2100-11			ML	
00169-7501-11			ML	
00169-6339-10			ML	

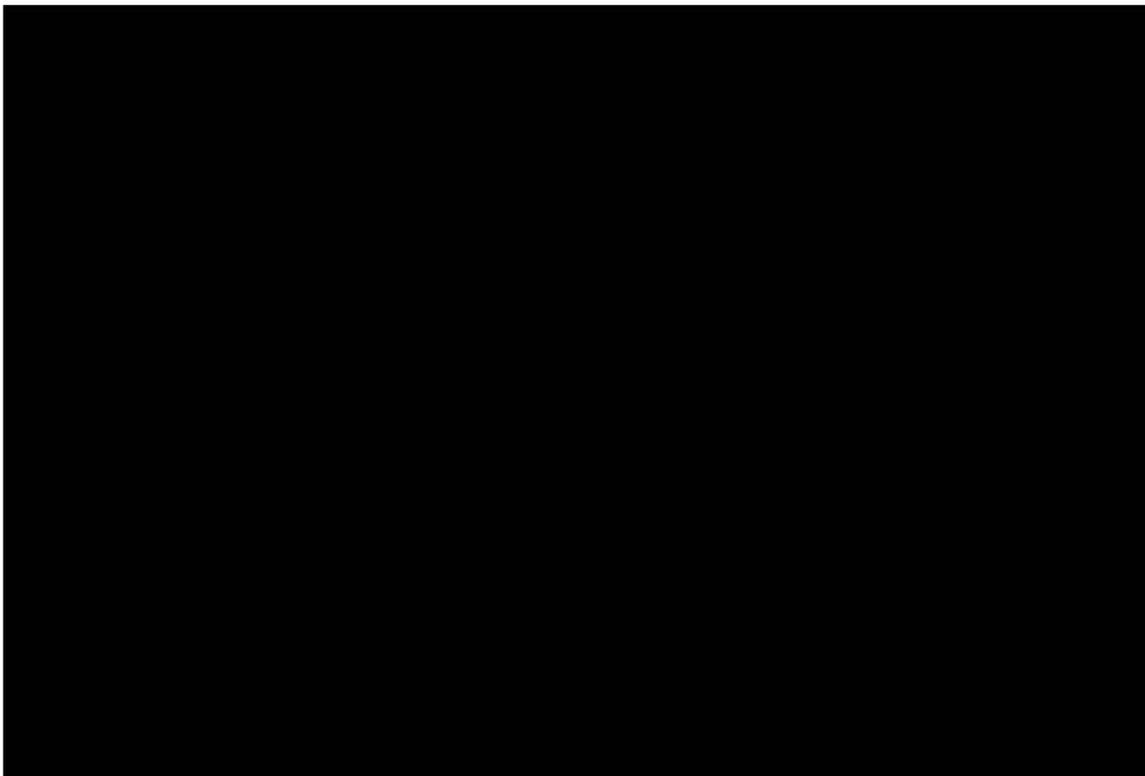
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We have included data and information according to NDC in order to comply with CMS’s instructions in good faith. However, we note that the NovoLog® and Fiasp® products are distinct drug products with separate unit production and distribution costs.

CMS's list of NDCs of selected drugs includes NDCs for unbranded biologic versions of certain Novo Nordisk products marketed by Novo Nordisk Pharma, Inc. (NNPI). NNPI qualifies as a "Secondary Manufacturer" under CMS's definition as set forth in the ICR. The methodology described below for purposes of developing unit cost of production and distribution applies to both Novo Nordisk Inc. (NNI) and NNPI (collectively referred to hereinafter as "Novo Nordisk").

The response to Question 7 contains unit costs of production and distribution at the mL level in accordance with the ICR instructions. [REDACTED]

Per Pack Production Cost and Distribution Cost:



In developing the production unit cost calculation, the following cost elements were included:

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

In developing the distribution unit cost calculation, the following cost elements were included:

[Redacted]

Other Assumptions:

The current unit costs of production and distribution are based on all in-scope NDCs produced by Novo Nordisk Inc. and Novo Nordisk Pharma, Inc. for the United States between June 1, 2022, and May 31, 2023,

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

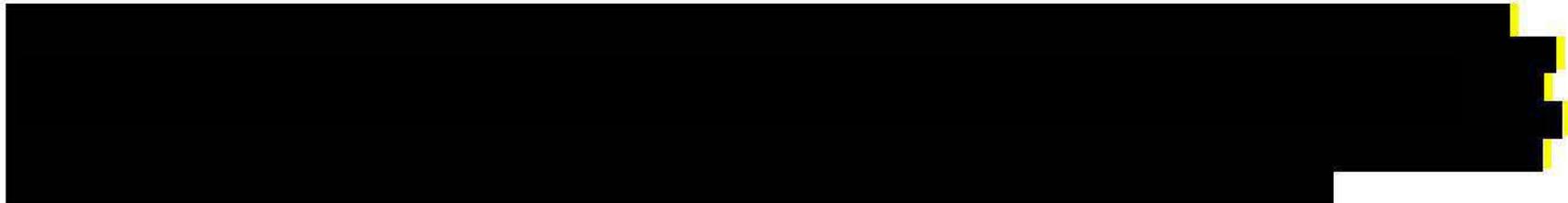
[REDACTED]

Novo Nordisk has limited the unit cost of production and distribution to those products identified by CMS for sale in the U.S., consistent with the ICR guidance that provides current unit costs of production and distribution of the selected drug are defined to include, in relevant part, “[o]nly units (and associated costs) produced and distributed for U.S. sales.” For this reason, Novo Nordisk is not reporting data on the following NDCs that are samples, inner NDCs for samples, or are otherwise provided at no charge, and akin to a sample, as these products are never sold in the U.S.:

00169320190
00169320490

00169320497
00169320591
00169320595
00169320691
00169320695
00169330390
00169330391
00169633890
00169633897
00169633990
00169633997
00169633998
00169750190
00169200190

Novo Nordisk did not report on any NDCs related to Fiasp PumpCart as the product was not launched until September 2023, and thus, it is outside the temporal scope for Section D.



The total unit volume reported in response to Question 7 represents the number of packs that have been delivered from Novo Nordisk's warehouse to customers for each of the selected NDCs during the applicable period.

The cost elements do not reflect investments made to production outside the period between June 2022 through May 2023 and therefore create an inaccurate, narrow snapshot of the costs incurred by Novo Nordisk to produce and distribute these products without contemplation of significant past or future investments in the production and distribution of these products. Indeed, Novo Nordisk is continuously expanding our global manufacturing network to meet the needs of our patients worldwide across multiple therapy areas. Novo Nordisk currently has investment projects to build, ramp-up and increase production capacity totaling 25bDKK globally.

When calculating and reporting monetary amounts, Novo Nordisk used International Financial Reporting Standards (IFRS), as those are the company's established accounting standards.

Novo Nordisk utilized the Federal Reserve Bank conversion rates to convert DKK to USD. The exchange rate calculation is split into two periods from June 1, 2022 through December 31, 2022 and January 1, 2023 through May 31, 2023.

E. Federal Financial Support				
<p>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.</p>				
Total Federal Financial Support	Federal Financial Support	Type of Agreement	Federal Agency(ies) Participating in Agreement	Nature of Agreement
	<p>This response (along with the related response to Question 9) contains trade secret and confidential commercial and financial information that Novo Nordisk customarily and actually treats as private. Disclosure of this information would result in harm to Novo Nordisk's business interests, including because disclosure of any individual piece(s) of information could result in public identification of confidential materials. Novo Nordisk submits this information under CMS's assurances of confidentiality (Guidance § 40.2.1 (citing id. § 40.2.2; 5 U.S.C. § 552(b)(3), (4); 18 U.S.C. § 1905)) and designates this submission as confidential and exempt from disclosure under Exemption 4 of the FOIA (45 C.F.R. 5.41). As such, predisclosure notification is required (45 C.F.R. 5.42). Novo Nordisk's future disclosure of any piece of the information contained herein and designated as confidential does not alter the status of the remaining information as exempt from disclosure or otherwise waive or forfeit Novo Nordisk's rights to confidential treatment and predisclosure notification.</p>	OTH		

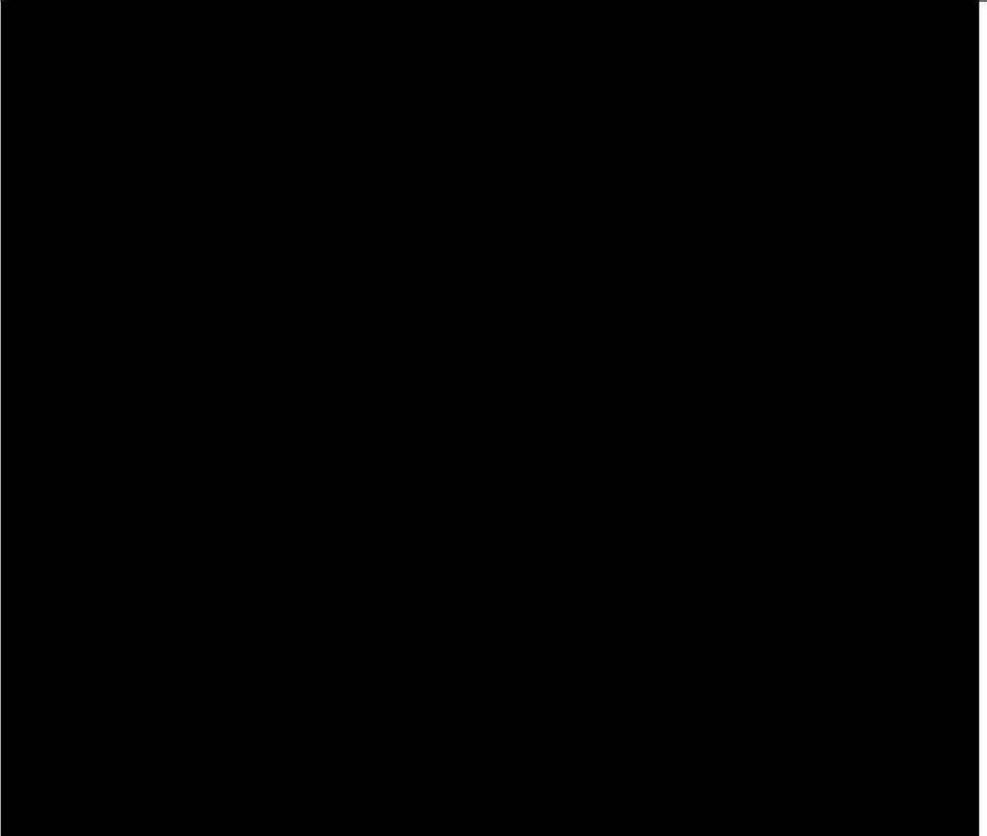
E. Federal Financial Support

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

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
				

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

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
	<div data-bbox="350 594 1331 813" style="background-color: black; width: 100%; height: 135px; margin-bottom: 10px;"></div> <p data-bbox="350 841 1331 1117">As detailed above, Novo Nordisk received minimal federal financial support [REDACTED] for the therapeutic discovery and development of NovoLog® and FIASP®. As a company, Novo Nordisk has been focused on diabetes treatment for over 100 years, and while other companies are scaling back their commitments, we continue to make significant investments in developing revolutionary new insulin therapies. Our longstanding experience in R&D for patients living with diabetes has helped us to grow organically and fund our own research, including late-stage trials, which receive no funding from US government agencies like the National Institutes of Health.</p> <p data-bbox="350 1159 1331 1364">In fact, Novo Nordisk through its majority shareholder, the Novo Nordisk Foundation, is itself a supporter of biomedical R&D as a grant-maker and research partner for external organizations in the US and beyond. Between 2018 and 2022, the Foundation provided \$111 million in financing for R&D projects from US applicants and over \$1.9 billion towards physiological, endocrinological, metabolic and other biomedical research globally.</p> <p data-bbox="350 1406 1331 1433">The Novo Nordisk Foundation is among the top five largest grant-making charitable</p>			

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
	<p>foundations in the world. Among its key objectives is to progress research and innovation in the prevention and treatment of cardiometabolic and infectious diseases, including by providing direct support for the development of new medicines and other clinical aids and interventions. Critically, the Foundation also supports initiatives to improve the understanding of disease mechanisms, thereby paving the way for new, patient-centered approaches to detecting, managing and treating cardiometabolic disease.</p> <p>A major focus of the Novo Nordisk Foundation’s mission is to invest in scientific research, education, and innovation more broadly to enable a world class life science ecosystem which fosters scientific breakthroughs and the development of new technologies. Grants from the Foundation invest across the entire life science value chain and support capacity building, including the development of a diverse and inclusive academic community; international cooperation in the sciences; and cross- and inter-disciplinary collaboration. The Foundation supports both curiosity-driven research and research that is translational or mission-driven in areas such as data and material sciences, AI, genomics, robotics, quantum technologies, and microbiome and systems biology, among others.</p> <p>Supporting biomedical and clinical science with a particular focus on diabetes and its comorbidities has been part of the Novo Nordisk Foundation legacy for the last century. Building on this legacy, the Foundation has increased its support for research on the prevention and treatment of cardiometabolic diseases: diabetes, obesity, and cardiovascular disease, and the consequences of this cluster of common and complex diseases. Addressing inequity in health is also a cross-cutting theme for the Foundation in its support of health-promoting interventions.</p>			

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
	<p>Though the R&D ecosystem is global, and the benefits of technological advancements are not confined by geography, the Novo Nordisk Foundation has been a significant contributor to R&D projects originating in the US. In 2022 alone, the Novo Nordisk Foundation funded US-based projects from 13 senior researchers and 52 young researchers, PhD students, and postdoctoral students. Moreover, Foundation grantees have collaborated extensively with more than 850 American research institutions, 277 of which are major universities or university hospitals, including Harvard University and the Cleveland Clinic, as well as UC Davis, and Carnegie Mellon to name a few. This collaborative research has led to over 2,500 highly cited publications in peer-reviewed scientific journals. Researchers receiving grants from the Novo Nordisk Foundation also collaborate with over 200 US companies, the majority of which are in the biotechnology or pharmaceutical sector, through participation in formalized R&D projects or by co-authoring open-source scientific publications. Approximately 20% of these companies are in the medical device, medical information technology, hospital, or health care sector.</p>			

Explanations: Please note we are only selecting “other” under “Type of Agreement” because the HPMS system will not allow us to leave blank or provide a response which states that Novo Nordisk, Inc. (NNI) has no licensing agreement, pricing agreement, purchasing agreement, or other agreement in place with any federal government agency related to the discovery, research, and/or development of NovoLog® or FIASP®.

NNI has no licensing agreement, pricing agreement, purchasing agreement, or other agreement in place with any federal government agency related to the discovery, research, and/or development of NovoLog® or FIASP®.

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
5,618,913	1986-08-29	2014-12-07	N	Y	N	N	UTL	Y
5,626,566	1992-09-07	2014-11-06	N	N	N	N	UTL	Y
5,693,027	1994-09-26	2014-12-02	N	N	N	N	UTL	Y
5,866,538	1997-06-20	2017-12-20	Y	N	N	N	UTL	Y
7,762,994	2007-07-16	2024-05-23	N	N	N	N	UTL	Y
8,579,869	2012-02-10	2023-06-30	N	N	N	N	UTL	Y

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
6,004,297	1999-01-28	2019-07-28	N	N	N	N	UTL	Y
9,265,893	2008-01-21	2032-09-23	N	N	N	N	UTL	Y
RE 41,956	2005-05-04	2021-01-21	N	N	N	N	UTL	Y
RE 43,834	2003-05-21	2019-01-28	N	N	N	N	UTL	Y
6,899,699	2002-01-02	2022-01-02	N	N	N	N	UTL	Y
8,672,898	2004-10-22	2022-01-02	N	N	N	N	UTL	Y
8,684,969	2012-09-25	2025-10-20	N	N	N	N	UTL	Y
8,920,383	2008-06-02	2026-07-17	N	N	N	N	UTL	Y
9,108,002	2011-12-15	2026-01-20	N	N	N	N	UTL	Y
9,132,239	2011-08-01	2032-02-01	N	N	N	N	UTL	Y
9,457,154	2008-07-09	2027-09-27	N	N	N	N	UTL	Y
9,486,588	2014-01-30	2022-01-02	N	N	N	N	UTL	Y
9,616,180	2015-07-13	2026-01-20	N	N	N	N	UTL	Y

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
9,687,611	2014-01-29	2025-10-20	N	N	N	N	UTL	Y
9,775,953	2014-11-21	2026-07-17	N	N	N	N	UTL	Y
9,861,757	2016-08-19	2026-01-20	N	N	N	N	UTL	Y
10,220,155	2008-03-20	2026-07-17	N	N	N	N	UTL	Y
10,357,616	2017-11-17	2026-01-20	N	N	N	N	UTL	Y
10,376,652	2017-02-24	2026-01-20	N	N	N	N	UTL	Y
RE 46,363	2013-11-27	2026-08-03	N	N	N	N	UTL	Y

Explanations: The information contained within this response, along with responses to questions 12, 14, and 15, contains confidential commercial and financial information that Novo Nordisk customarily and actually treats as private. Disclosure of this information would result in harm to Novo Nordisk's business interests, including because disclosure of any individual piece(s) of information could result in public identification of confidential materials. Novo Nordisk submits this information under CMS's assurances of confidentiality (Guidance § 40.2.1 (citing id. § 40.2.2; 5 U.S.C. § 552(b)(3), (4); 18 U.S.C. § 1905)) and designates this submission as confidential and exempt from disclosure under Exemption 4 of the FOIA (45 C.F.R. 5.41). As such, predisclosure notification is required (45 C.F.R. 5.42). Novo Nordisk's future disclosure of any piece of the information contained herein and designated as confidential does not alter the status of the remaining information as exempt from disclosure or otherwise waive or forfeit Novo Nordisk's rights to confidential treatment and predisclosure notification.

Regarding patent US5,693,027, the application number of which is 08/313,651, the document of the original U.S. Patent Application could not be obtained. NNI does not have such application on file and the US Patent and Trademark Office (USPTO) has informed NNI that the USPTO has destroyed the original patent application. In lieu of the U.S. Patent Application, NNI has uploaded the Patent Cooperation Treaty (PCT) application (PCT/DK91/00282), to which application 08/313,651 claimed priority.

[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	2005-12-07	20986	00169-7501, 00169-6339, 00169-3303	Extended by pediatric exclusivity. The following applies to all entries in this question: The NovoLog and Fiasp products were not licensed under the Public Health Services Act; they were approved under the Federal Food, Drug, and Cosmetic Act and were subsequently transitioned to approved biologics licenses as a result of the Biologics Price Competition and Innovation Act. BPCIA § 7002(e)(4). In response to Question 14, we have included the original Orange Book expiration dates.
PED	2005-12-07	20986	00169-7501, 00169-6339, 00169-3303	Extension of NCE exclusivity
CIE	2004-12-21	20986	00169-7501	
CIE	2009-03-13	20986	00169-7501, 00169-6339, 00169-3303	Extended by pediatric exclusivity
PED	2009-03-13	20986	00169-7501, 00169-6339, 00169-3303	Extension of NCI exclusivity
CIE	2011-03-14	20986	00169-7501	
CIE	2020-09-29	208751	00169-3201, 00169-3204	
CIE	2022-10-21	208751	00169-3201	

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	2022-12-19	208751	00169-3201, 00169-3204, 00169-3205	

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
20986	BLA		2000-06-07	the treatment of adult patients with	Subcutaneous injection 10 mL	Novo Nordisk, Inc.	APP	Original NDA. The following note applies

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
				diabetes mellitus, for the control of hyperglycemia	vial (100 units/mL) 3 mL PenFill cartridge (100 units/mL)			to all BLAs listed in this table: The NovoLog and Fiasp products identified in this response were not licensed in BLAs under the Public Health Service Act; they were approved in NDAs under the Federal Food, Drug, and Cosmetic Act and were subsequently transitioned to approved biological product licenses as a result of the Biologics Price Competition and Innovation Act of 2009 (BPCIA § 7002(e)(4)).

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
20986	BLA		2001-12-21	the treatment of adult patients with diabetes mellitus, for the control of hyperglycemia	10 mL vial (100 units/mL)	Novo Nordisk, Inc.	APP	Supplement. Dosage and Administration section of PI broadened to include Continuous subcutaneous infusion (external insulin infusion pumps)
20986	BLA		2002-12-04	the treatment of adult patients with diabetes mellitus, for the control of hyperglycemia	FlexPen autoinjector 3 mL (100 units/mL) 10 mL vial (100 units/mL) 3 mL PenFill cartridge (100 units/mL)	Novo Nordisk, Inc.	APP	Supplement. Clinical Pharmacology section of PI revised to modify Obesity, Renal Impairment, and Hepatic Impairment subsections (PHASE IV Commitment)
20986	BLA		2005-09-13	the treatment of patients with diabetes mellitus,	FlexPen autoinjector 3 mL (100 units/mL) 10 mL	Novo Nordisk, Inc.	APP	Supplement. Precautions section of PI updated to revise Pediatric Use

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
				for the control of hyperglycemia	vial (100 units/mL) 3 mL PenFill cartridge (100 units/mL)			subsection (Written Request)
20986	BLA		2005-10-21	the treatment of patients with diabetes mellitus, for the control of hyperglycemia	10 mL vial (100 units/mL)	Novo Nordisk, Inc.	APP	Supplement. PI updated to allow for intravenous administration
20986	BLA		2007-01-26	the treatment of patients with diabetes mellitus, for the control of hyperglycemia	FlexPen autoinjector 3 mL (100 units/mL) 10 mL vial (100 units/mL) 3 mL PenFill cartridge (100 units/mL)	Novo Nordisk, Inc.	APP	Supplement. Precautions section of the PI updated to change Pregnancy Category C to Pregnancy Category B
20986	BLA		2008-03-14	indicated to improve glycemic control in adults	10 mL vial (100 units/mL)	Novo Nordisk, Inc.	APP	Supplement. PI updated to include pediatric use of continuous

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
				and children with diabetes mellitus				subcutaneous insulin infusion (external insulin infusion pumps)
208751	BLA		2017-09-29	rapid-acting insulin indicated to improve glycemic control in adult with diabetes mellitus	FlexTouch Pen 3 mL (100 units/mL) 10 mL vial (100 units/mL)	Novo Nordisk, Inc.	APP	Original NDA
208751	BLA		2019-10-21	rapid-acting insulin indicated to improve glycemic control in adult with diabetes mellitus	10 mL vial (100 units/mL)	Novo Nordisk, Inc.	APP	Supplement. Dosage and Administration section of PI broadened to include continuous subcutaneous insulin infusion (CSII)
208751	BLA		2019-12-19	rapid-acting human insulin analog indicated to improve glycemic control in adult and	FlexTouch Pen 3 mL (100 units/mL) 10 mL vial (100 units/mL) 3 mL	Novo Nordisk, Inc.	APP	Supplement. PI updated to include pediatric indication and addition of CSII use in pediatric

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
				pediatric patients with diabetes mellitus	PenFill cartridge (100 units/mL)			patients (PHASE IV Commitment)

Explanations: None.

G. Market Data and Revenue and Sales Volume Data

Wholesale Acquisition Cost Unit Price

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

National Drug Code (NDC-11)	Quarter	WAC	Unit type (each, ML, GM)	Total Unit Volume
00169-3303-12	2018-Q3	\$35.83	ML	
00169-3303-12	2018-Q4	\$35.83	ML	
00169-3303-12	2019-Q1	\$35.83	ML	
00169-3303-12	2019-Q2	\$35.83	ML	

G. Market Data and Revenue and Sales Volume Data

Wholesale Acquisition Cost Unit Price

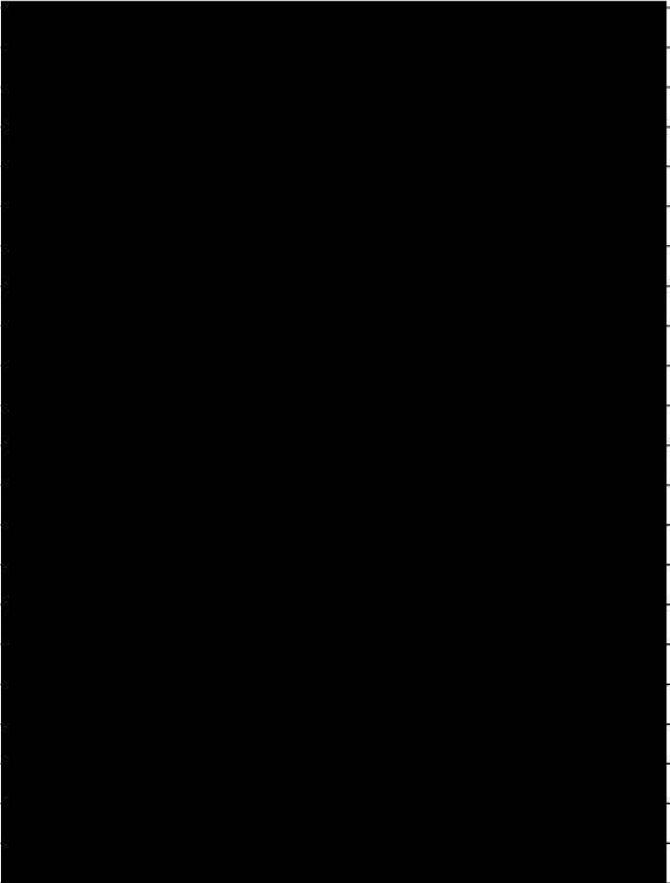
Description: The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Wholesale Acquisition Cost (WAC) unit price of the selected drug.

National Drug Code (NDC-11)	Quarter	WAC	Unit type (each, ML, GM)	Total Unit Volume
00169-3303-12	2019-Q3	\$35.83	ML	[REDACTED]
00169-3303-12	2019-Q4	\$35.83	ML	
00169-3303-12	2020-Q1	\$35.83	ML	
00169-3303-12	2020-Q2	\$35.83	ML	
00169-3303-12	2020-Q3	\$35.83	ML	
00169-3303-12	2020-Q4	\$35.83	ML	
00169-3303-12	2021-Q1	\$35.83	ML	
00169-3303-12	2021-Q2	\$35.83	ML	
00169-3303-12	2021-Q3	\$35.83	ML	
00169-3303-12	2021-Q4	\$35.83	ML	
00169-3303-12	2022-Q1	\$35.83	ML	
00169-3303-12	2022-Q2	\$35.83	ML	
00169-3303-12	2022-Q3	\$35.83	ML	
00169-3303-12	2022-Q4	\$35.83	ML	
00169-6339-10	2018-Q3	\$37.26	ML	
00169-6339-10	2018-Q4	\$37.26	ML	
00169-6339-10	2019-Q1	\$37.26	ML	
00169-6339-10	2019-Q2	\$37.26	ML	
00169-6339-10	2019-Q3	\$37.26	ML	
00169-6339-10	2019-Q4	\$37.26	ML	
00169-6339-10	2020-Q1	\$37.26	ML	
00169-6339-10	2020-Q2	\$37.26	ML	

G. Market Data and Revenue and Sales Volume Data

Wholesale Acquisition Cost Unit Price

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

National Drug Code (NDC-11)	Quarter	WAC	Unit type (each, ML, GM)	Total Unit Volume
00169-6339-10	2020-Q3	\$37.26	ML	
00169-6339-10	2020-Q4	\$37.26	ML	
00169-6339-10	2021-Q1	\$37.26	ML	
00169-6339-10	2021-Q2	\$37.26	ML	
00169-6339-10	2021-Q3	\$37.26	ML	
00169-6339-10	2021-Q4	\$37.26	ML	
00169-6339-10	2022-Q1	\$37.26	ML	
00169-6339-10	2022-Q2	\$37.26	ML	
00169-6339-10	2022-Q3	\$37.26	ML	
00169-6339-10	2022-Q4	\$37.26	ML	
00169-7501-11	2018-Q3	\$28.94	ML	
00169-7501-11	2018-Q4	\$28.94	ML	
00169-7501-11	2019-Q1	\$28.94	ML	
00169-7501-11	2019-Q2	\$28.94	ML	
00169-7501-11	2019-Q3	\$28.94	ML	
00169-7501-11	2019-Q4	\$28.94	ML	
00169-7501-11	2020-Q1	\$28.94	ML	
00169-7501-11	2020-Q2	\$28.94	ML	
00169-7501-11	2020-Q3	\$28.94	ML	
00169-7501-11	2020-Q4	\$28.94	ML	
00169-7501-11	2021-Q1	\$28.94	ML	
00169-7501-11	2021-Q2	\$28.94	ML	

G. Market Data and Revenue and Sales Volume Data

Wholesale Acquisition Cost Unit Price

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

National Drug Code (NDC-11)	Quarter	WAC	Unit type (each, ML, GM)	Total Unit Volume
00169-7501-11	2021-Q3	\$28.94	ML	
00169-7501-11	2021-Q4	\$28.94	ML	
00169-7501-11	2022-Q1	\$28.94	ML	
00169-7501-11	2022-Q2	\$28.94	ML	
00169-7501-11	2022-Q3	\$28.94	ML	
00169-7501-11	2022-Q4	\$28.94	ML	
00169-3201-11	2018-Q3	\$28.94	ML	
00169-3201-11	2018-Q4	\$28.94	ML	
00169-3201-11	2019-Q1	\$28.94	ML	
00169-3201-11	2019-Q2	\$28.94	ML	
00169-3201-11	2019-Q3	\$28.94	ML	
00169-3201-11	2019-Q4	\$28.94	ML	
00169-3201-11	2020-Q1	\$28.94	ML	
00169-3201-11	2020-Q2	\$28.94	ML	
00169-3201-11	2020-Q3	\$28.94	ML	
00169-3201-11	2020-Q4	\$28.94	ML	
00169-3201-11	2021-Q1	\$28.94	ML	
00169-3201-11	2021-Q2	\$28.94	ML	
00169-3201-11	2021-Q3	\$28.94	ML	
00169-3201-11	2021-Q4	\$28.94	ML	
00169-3201-11	2022-Q1	\$28.94	ML	
00169-3201-11	2022-Q2	\$28.94	ML	

G. Market Data and Revenue and Sales Volume Data

Wholesale Acquisition Cost Unit Price

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

National Drug Code (NDC-11)	Quarter	WAC	Unit type (each, ML, GM)	Total Unit Volume
00169-3201-11	2022-Q3	\$28.94	ML	[REDACTED]
00169-3201-11	2022-Q4	\$28.94	ML	
00169-3204-15	2018-Q3	\$37.26	ML	
00169-3204-15	2018-Q4	\$37.26	ML	
00169-3204-15	2019-Q1	\$37.26	ML	
00169-3204-15	2019-Q2	\$37.26	ML	
00169-3204-15	2019-Q3	\$37.26	ML	
00169-3204-15	2019-Q4	\$37.26	ML	
00169-3204-15	2020-Q1	\$37.26	ML	
00169-3204-15	2020-Q2	\$37.26	ML	
00169-3204-15	2020-Q3	\$37.26	ML	
00169-3204-15	2020-Q4	\$37.26	ML	
00169-3204-15	2021-Q1	\$37.26	ML	
00169-3204-15	2021-Q2	\$37.26	ML	
00169-3204-15	2021-Q3	\$37.26	ML	
00169-3204-15	2021-Q4	\$37.26	ML	
00169-3204-15	2022-Q1	\$37.26	ML	
00169-3204-15	2022-Q2	\$37.26	ML	
00169-3204-15	2022-Q3	\$37.26	ML	
00169-3204-15	2022-Q4	\$37.26	ML	
00169-3205-15	2019-Q4	\$35.83	ML	
00169-3205-15	2020-Q1	\$35.83	ML	

G. Market Data and Revenue and Sales Volume Data

Wholesale Acquisition Cost Unit Price

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

National Drug Code (NDC-11)	Quarter	WAC	Unit type (each, ML, GM)	Total Unit Volume
00169-3205-15	2020-Q2	\$35.83	ML	
00169-3205-15	2020-Q3	\$35.83	ML	
00169-3205-15	2020-Q4	\$35.83	ML	
00169-3205-15	2021-Q1	\$35.83	ML	
00169-3205-15	2021-Q2	\$35.83	ML	
00169-3205-15	2021-Q3	\$35.83	ML	
00169-3205-15	2021-Q4	\$35.83	ML	
00169-3205-15	2022-Q1	\$35.83	ML	
00169-3205-15	2022-Q2	\$35.83	ML	
00169-3205-15	2022-Q3	\$35.83	ML	
00169-3205-15	2022-Q4	\$35.83	ML	
73070-0100-11	2019-Q4	\$14.47	ML	
73070-0100-11	2020-Q1	\$14.47	ML	
73070-0100-11	2020-Q2	\$14.47	ML	
73070-0100-11	2020-Q3	\$14.47	ML	
73070-0100-11	2020-Q4	\$14.47	ML	
73070-0100-11	2021-Q1	\$14.47	ML	
73070-0100-11	2021-Q2	\$14.47	ML	
73070-0100-11	2021-Q3	\$14.47	ML	
73070-0100-11	2021-Q4	\$14.47	ML	
73070-0100-11	2022-Q1	\$14.47	ML	
73070-0100-11	2022-Q2	\$14.47	ML	

G. Market Data and Revenue and Sales Volume Data

Wholesale Acquisition Cost Unit Price

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

National Drug Code (NDC-11)	Quarter	WAC	Unit type (each, ML, GM)	Total Unit Volume
73070-0100-11	2022-Q3	\$14.47	ML	[REDACTED]
73070-0100-11	2022-Q4	\$14.47	ML	
73070-0102-15	2019-Q4	\$17.92	ML	
73070-0102-15	2020-Q1	\$17.92	ML	
73070-0102-15	2020-Q2	\$17.92	ML	
73070-0102-15	2020-Q3	\$17.92	ML	
73070-0102-15	2020-Q4	\$17.92	ML	
73070-0102-15	2021-Q1	\$17.92	ML	
73070-0102-15	2021-Q2	\$17.92	ML	
73070-0102-15	2021-Q3	\$17.92	ML	
73070-0102-15	2021-Q4	\$17.92	ML	
73070-0102-15	2022-Q1	\$17.92	ML	
73070-0102-15	2022-Q2	\$17.92	ML	
73070-0102-15	2022-Q3	\$17.92	ML	
73070-0102-15	2022-Q4	\$17.92	ML	
73070-0103-15	2019-Q4	\$18.63	ML	
73070-0103-15	2020-Q1	\$18.63	ML	
73070-0103-15	2020-Q2	\$18.63	ML	
73070-0103-15	2020-Q3	\$18.63	ML	
73070-0103-15	2020-Q4	\$18.63	ML	
73070-0103-15	2021-Q1	\$18.63	ML	
73070-0103-15	2021-Q2	\$18.63	ML	

G. Market Data and Revenue and Sales Volume Data

Wholesale Acquisition Cost Unit Price

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

National Drug Code (NDC-11)	Quarter	WAC	Unit type (each, ML, GM)	Total Unit Volume
73070-0103-15	2021-Q3	\$18.63	ML	
73070-0103-15	2021-Q4	\$18.63	ML	
73070-0103-15	2022-Q1	\$18.63	ML	
73070-0103-15	2022-Q2	\$18.63	ML	
73070-0103-15	2022-Q3	\$18.63	ML	
73070-0103-15	2022-Q4	\$18.63	ML	
00169-3303-12	2023-Q1	\$35.83	ML	
00169-3303-12	2023-Q2	\$35.83	ML	
00169-6339-10	2023-Q1	\$37.26	ML	
00169-6339-10	2023-Q2	\$37.26	ML	
00169-7501-11	2023-Q1	\$28.94	ML	
00169-7501-11	2023-Q2	\$28.94	ML	
00169-3201-11	2023-Q1	\$28.94	ML	
00169-3201-11	2023-Q2	\$28.94	ML	
00169-3204-15	2023-Q1	\$37.26	ML	
00169-3204-15	2023-Q2	\$37.26	ML	
00169-3205-15	2023-Q1	\$35.83	ML	
00169-3205-15	2023-Q2	\$35.83	ML	
73070-0100-11	2023-Q1	\$14.47	ML	
73070-0100-11	2023-Q2	\$14.47	ML	
73070-0102-15	2023-Q1	\$17.92	ML	
73070-0102-15	2023-Q2	\$17.92	ML	

G. Market Data and Revenue and Sales Volume Data

Wholesale Acquisition Cost Unit Price

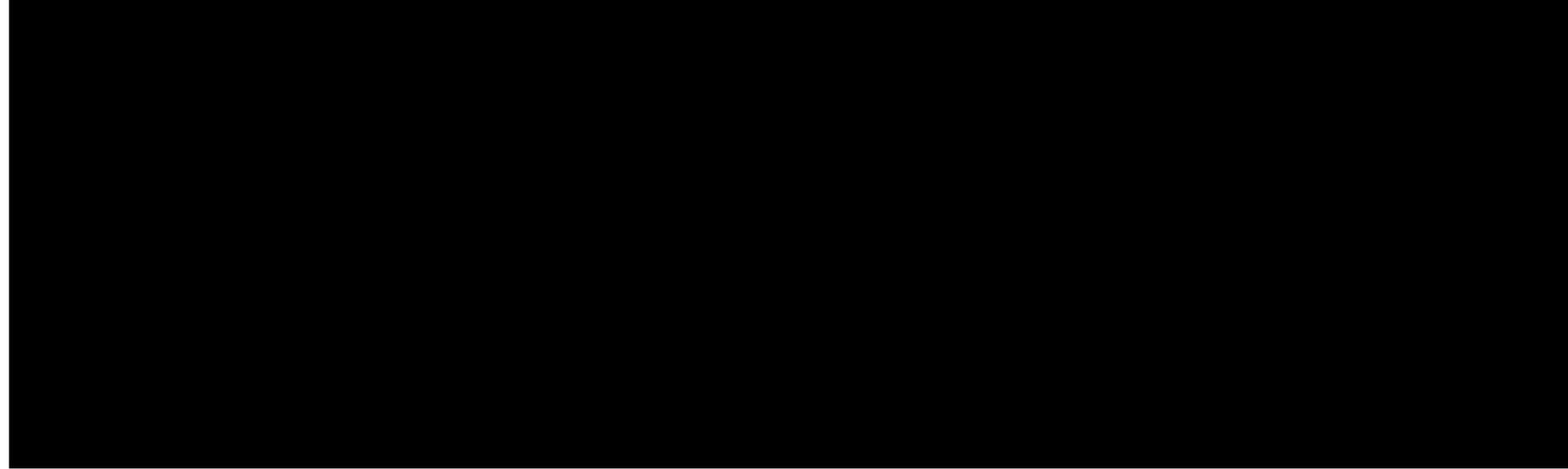
Description: The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Wholesale Acquisition Cost (WAC) unit price of the selected drug.

National Drug Code (NDC-11)	Quarter	WAC	Unit type (each, ML, GM)	Total Unit Volume
73070-0103-15	2023-Q1	\$18.63	ML	
73070-0103-15	2023-Q2	\$18.63	ML	

Explanations:

- a. This response contains trade secret and confidential commercial and financial information that Novo Nordisk customarily and actually treats as private. Disclosure of this information would result in harm to Novo Nordisk’s business interests, including because disclosure of any individual piece(s) of information could result in public identification of confidential materials. Novo Nordisk submits this information under CMS’s assurances of confidentiality (Guidance § 40.2.1 (citing id. § 40.2.2; 5 U.S.C. § 552(b)(3), (4); 18 U.S.C. § 1905)) and designates this submission as confidential and exempt from disclosure under Exemption 4 of the FOIA (45 C.F.R. 5.41). As such, predisclosure notification is required (45 C.F.R. 5.42). Novo Nordisk’s future disclosure of any piece of the information contained herein and designated as confidential does not alter the status of the remaining information as exempt from disclosure or otherwise waive or forfeit Novo Nordisk’s rights to confidential treatment and predisclosure notification.
- b. Reported WACs are those applicable to each NDC-11 at the close of the last day of each calendar quarter (i.e., March 31, June 30, September 30, and December 31). Reported WACs are not averaged across multiple values in a quarter. If there were a WAC change mid-quarter for a particular NDC-11, only the WAC in effect at the end of the calendar quarter is reported in response to Question 16.
- c. Reported WACs are presented at the milliliter (ML) level, consistent with the ICR request for Unit Type in Question 16. Reported WACs must be multiplied by the number of MLs in each NDC-11 package to match the WACs listed in drug databases, which are published at the NDC-11 level.
- d. WACs are not reported for non-saleable or inapplicable NDC-11s, including, but not limited to, inner packages, samples, [REDACTED] [REDACTED]. In addition, as explained further below, Novo Nordisk does not report WACs for NDCs of products repackaged by entities who do not qualify as “Secondary Manufacturers” under the ICR. Please see below for the list of NDCs for which Novo Nordisk is not reporting data.

- e. Total Unit Volume equals the total number of units (specifically, MLs) sold to direct purchasers in each quarter. [REDACTED]
- f. Consistent with the instructions for Question 16, when an NDC-11 was not marketed, sold, or distributed in a quarter, Novo Nordisk has left the WAC field blank and responded with "0" in the Total Unit Volume Field.
- g. CMS's list of NDCs of selected drugs includes NDCs for unbranded biologic versions of Novo Nordisk products marketed by Novo Nordisk Pharma, Inc. (NNPI). NNPI qualifies as a "Secondary Manufacturer" under CMS's definition as set forth in the ICR.



- i. The list of NDCs for which Novo Nordisk is not reporting data is set forth below:

NDC-11	Reason for Exclusion
00169200190	Diluent provided for no charge at physician request; akin to a sample
[REDACTED]	[REDACTED]
00169320190	Non-saleable sample
00169320490	Non-saleable inner NDC for Non-saleable sample
00169320497	Non-saleable sample
00169320511	Non-saleable inner NDC
00169320591	Non-saleable inner NDC for Non-saleable sample
00169320595	Non-saleable sample
00169320611	Non-saleable inner NDC

00169320691	Non-saleable inner NDC for Non-saleable sample
00169320695	Non-saleable sample)
00169330390	Non-saleable sample; discontinued
00169330391	Non-saleable sample; discontinued
00169633890	Non-saleable inner NDC for Non-saleable sample; never launched
00169633897	Non-saleable sample; never launched
00169633990	Non-saleable inner NDC for Non-saleable sample
00169633997	Non-saleable sample
00169633998	Non-saleable sample
00169750190	Non-saleable sample



73070010210	Non-saleable inner NDC
73070010310	Non-saleable inner NDC

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	00169-2100	2023-Q2		ML	
Y	00169-2100	2023-Q1		ML	
Y	00169-2100	2022-Q4		ML	
Y	00169-2100	2022-Q3		ML	
Y	00169-2100	2022-Q2		ML	
Y	00169-2100	2022-Q1		ML	
Y	00169-2100	2021-Q4		ML	
Y	00169-2100	2021-Q3		ML	
Y	00169-2100	2021-Q2		ML	
Y	00169-2101	2023-Q2		ML	
Y	00169-2101	2023-Q1		ML	
Y	00169-2101	2022-Q4		ML	
Y	00169-2101	2022-Q3		ML	
Y	00169-2101	2022-Q2		ML	
Y	00169-2101	2022-Q1		ML	
Y	00169-2101	2021-Q4		ML	
Y	00169-2101	2021-Q3		ML	
Y	00169-2101	2021-Q2		ML	
Y	00169-3201	2023-Q2		ML	
Y	00169-3201	2023-Q1		ML	

G. Market Data and Revenue and Sales Volume Data

Medicaid Best Price

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

Medicaid Best Price	National Drug Code (NDC-9)	Quarter	Medicaid Best Price	Unit Type	Total Unit Volume
Y	00169-3201	2022-Q4		ML	
Y	00169-3201	2022-Q3		ML	
Y	00169-3201	2022-Q2		ML	
Y	00169-3201	2022-Q1		ML	
Y	00169-3201	2021-Q4		ML	
Y	00169-3201	2021-Q3		ML	
Y	00169-3201	2021-Q2		ML	
Y	00169-3201	2021-Q1		ML	
Y	00169-3201	2020-Q4		ML	
Y	00169-3201	2020-Q3		ML	
Y	00169-3201	2020-Q2		ML	
Y	00169-3201	2020-Q1		ML	
Y	00169-3201	2019-Q4		ML	
Y	00169-3201	2019-Q3		ML	
Y	00169-3201	2019-Q2		ML	
Y	00169-3201	2019-Q1		ML	
Y	00169-3201	2018-Q4		ML	
Y	00169-3201	2018-Q3		ML	
Y	00169-3204	2023-Q2		ML	
Y	00169-3204	2023-Q1		ML	

G. Market Data and Revenue and Sales Volume Data

Medicaid Best Price

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

Medicaid Best Price	National Drug Code (NDC-9)	Quarter	Medicaid Best Price	Unit Type	Total Unit Volume
Y	00169-3204	2022-Q4		ML	
Y	00169-3204	2022-Q3		ML	
Y	00169-3204	2022-Q2		ML	
Y	00169-3204	2022-Q1		ML	
Y	00169-3204	2021-Q4		ML	
Y	00169-3204	2021-Q3		ML	
Y	00169-3204	2021-Q2		ML	
Y	00169-3204	2021-Q1		ML	
Y	00169-3204	2020-Q4		ML	
Y	00169-3204	2020-Q3		ML	
Y	00169-3204	2020-Q2		ML	
Y	00169-3204	2020-Q1		ML	
Y	00169-3204	2019-Q4		ML	
Y	00169-3204	2019-Q3		ML	
Y	00169-3204	2019-Q2		ML	
Y	00169-3204	2019-Q1		ML	
Y	00169-3204	2018-Q4		ML	
Y	00169-3204	2018-Q3		ML	
Y	00169-3205	2023-Q2		ML	
Y	00169-3205	2023-Q1		ML	

G. Market Data and Revenue and Sales Volume Data

Medicaid Best Price

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

Medicaid Best Price	National Drug Code (NDC-9)	Quarter	Medicaid Best Price	Unit Type	Total Unit Volume
Y	00169-3205	2022-Q4		ML	
Y	00169-3205	2022-Q3		ML	
Y	00169-3205	2022-Q2		ML	
Y	00169-3205	2022-Q1		ML	
Y	00169-3205	2021-Q4		ML	
Y	00169-3205	2021-Q3		ML	
Y	00169-3205	2021-Q2		ML	
Y	00169-3205	2021-Q1		ML	
Y	00169-3205	2020-Q4		ML	
Y	00169-3205	2020-Q3		ML	
Y	00169-3205	2020-Q2		ML	
Y	00169-3205	2020-Q1		ML	
Y	00169-3205	2019-Q4		ML	
Y	00169-3303	2023-Q2		ML	
Y	00169-3303	2023-Q1		ML	
Y	00169-3303	2022-Q4		ML	
Y	00169-3303	2022-Q3		ML	
Y	00169-3303	2022-Q2		ML	
Y	00169-3303	2022-Q1		ML	
Y	00169-3303	2021-Q4		ML	

G. Market Data and Revenue and Sales Volume Data

Medicaid Best Price

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

Medicaid Best Price	National Drug Code (NDC-9)	Quarter	Medicaid Best Price	Unit Type	Total Unit Volume
Y	00169-3303	2021-Q3		ML	
Y	00169-3303	2021-Q2		ML	
Y	00169-3303	2021-Q1		ML	
Y	00169-3303	2020-Q4		ML	
Y	00169-3303	2020-Q3		ML	
Y	00169-3303	2020-Q2		ML	
Y	00169-3303	2020-Q1		ML	
Y	00169-3303	2019-Q4		ML	
Y	00169-3303	2019-Q3		ML	
Y	00169-3303	2019-Q2		ML	
Y	00169-3303	2019-Q1		ML	
Y	00169-3303	2018-Q4		ML	
Y	00169-3303	2018-Q3		ML	
Y	00169-6339	2023-Q2		ML	
Y	00169-6339	2023-Q1		ML	
Y	00169-6339	2022-Q4		ML	
Y	00169-6339	2022-Q3		ML	
Y	00169-6339	2022-Q2		ML	
Y	00169-6339	2022-Q1		ML	
Y	00169-6339	2021-Q4		ML	

G. Market Data and Revenue and Sales Volume Data

Medicaid Best Price

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

Medicaid Best Price	National Drug Code (NDC-9)	Quarter	Medicaid Best Price	Unit Type	Total Unit Volume
Y	00169-6339	2021-Q3		ML	
Y	00169-6339	2021-Q2		ML	
Y	00169-6339	2021-Q1		ML	
Y	00169-6339	2020-Q4		ML	
Y	00169-6339	2020-Q3		ML	
Y	00169-6339	2020-Q2		ML	
Y	00169-6339	2020-Q1		ML	
Y	00169-6339	2019-Q4		ML	
Y	00169-6339	2019-Q3		ML	
Y	00169-6339	2019-Q2		ML	
Y	00169-6339	2019-Q1		ML	
Y	00169-6339	2018-Q4		ML	
Y	00169-6339	2018-Q3		ML	
Y	00169-7501	2023-Q2		ML	
Y	00169-7501	2023-Q1		ML	
Y	00169-7501	2022-Q4		ML	
Y	00169-7501	2022-Q3		ML	
Y	00169-7501	2022-Q2		ML	
Y	00169-7501	2022-Q1		ML	
Y	00169-7501	2021-Q4		ML	

G. Market Data and Revenue and Sales Volume Data

Medicaid Best Price

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

Medicaid Best Price	National Drug Code (NDC-9)	Quarter	Medicaid Best Price	Unit Type	Total Unit Volume
Y	00169-7501	2021-Q3		ML	
Y	00169-7501	2021-Q2		ML	
Y	00169-7501	2021-Q1		ML	
Y	00169-7501	2020-Q4		ML	
Y	00169-7501	2020-Q3		ML	
Y	00169-7501	2020-Q2		ML	
Y	00169-7501	2020-Q1		ML	
Y	00169-7501	2019-Q4		ML	
Y	00169-7501	2019-Q3		ML	
Y	00169-7501	2019-Q2		ML	
Y	00169-7501	2019-Q1		ML	
Y	00169-7501	2018-Q4		ML	
Y	00169-7501	2018-Q3		ML	
Y	73070-0100	2023-Q2		ML	
Y	73070-0100	2023-Q1		ML	
Y	73070-0100	2022-Q4		ML	
Y	73070-0100	2022-Q3		ML	
Y	73070-0100	2022-Q2		ML	
Y	73070-0100	2022-Q1		ML	
Y	73070-0100	2021-Q4		ML	

G. Market Data and Revenue and Sales Volume Data

Medicaid Best Price

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

Medicaid Best Price	National Drug Code (NDC-9)	Quarter	Medicaid Best Price	Unit Type	Total Unit Volume
Y	73070-0100	2021-Q3		ML	
Y	73070-0100	2021-Q2		ML	
Y	73070-0100	2021-Q1		ML	
Y	73070-0100	2020-Q4		ML	
Y	73070-0100	2020-Q3		ML	
Y	73070-0100	2020-Q2		ML	
Y	73070-0100	2020-Q1		ML	
Y	73070-0102	2023-Q2		ML	
Y	73070-0102	2023-Q1		ML	
Y	73070-0102	2022-Q4		ML	
Y	73070-0102	2022-Q3		ML	
Y	73070-0102	2022-Q2		ML	
Y	73070-0102	2022-Q1		ML	
Y	73070-0102	2021-Q4		ML	
Y	73070-0102	2021-Q3		ML	
Y	73070-0102	2021-Q2		ML	
Y	73070-0102	2021-Q1		ML	
Y	73070-0102	2020-Q4		ML	
Y	73070-0102	2020-Q3		ML	
Y	73070-0102	2020-Q2		ML	

G. Market Data and Revenue and Sales Volume Data

Medicaid Best Price

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

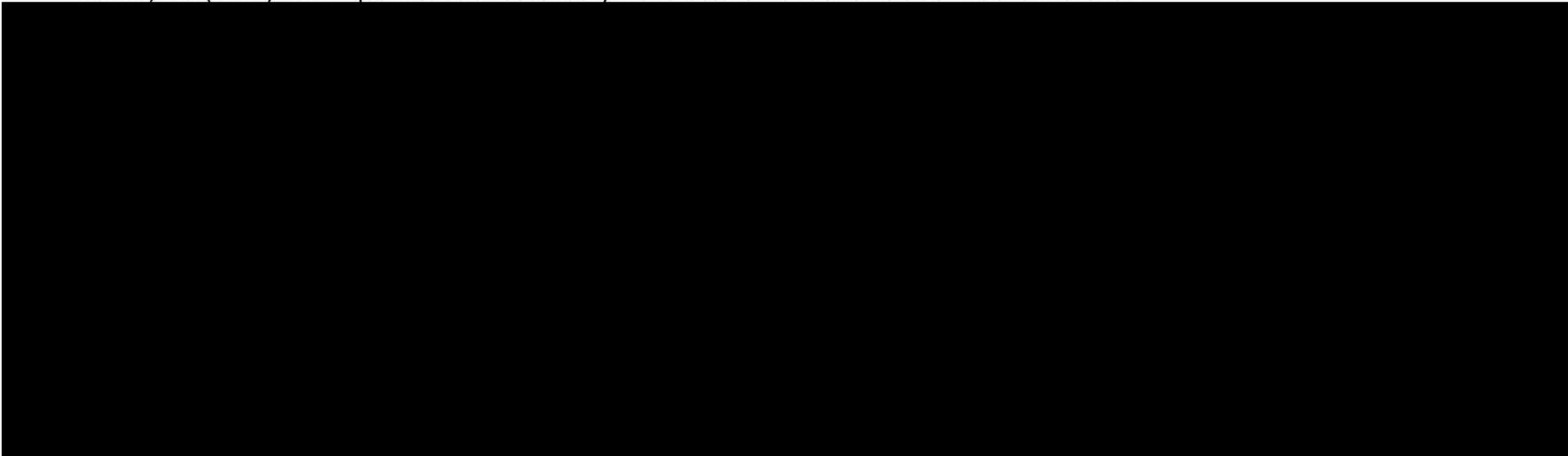
Medicaid Best Price	National Drug Code (NDC-9)	Quarter	Medicaid Best Price	Unit Type	Total Unit Volume
Y	73070-0102	2020-Q1		ML	
Y	73070-0103	2023-Q2		ML	
Y	73070-0103	2023-Q1		ML	
Y	73070-0103	2022-Q4		ML	
Y	73070-0103	2022-Q3		ML	
Y	73070-0103	2022-Q2		ML	
Y	73070-0103	2022-Q1		ML	
Y	73070-0103	2021-Q4		ML	
Y	73070-0103	2021-Q3		ML	
Y	73070-0103	2021-Q2		ML	
Y	73070-0103	2021-Q1		ML	
Y	73070-0103	2020-Q4		ML	
Y	73070-0103	2020-Q3		ML	
Y	73070-0103	2020-Q2		ML	
Y	73070-0103	2020-Q1		ML	

Explanations:

- a. This response contains trade secret and confidential commercial and financial information that Novo Nordisk customarily and actually treats as private. Disclosure of this information would result in harm to Novo Nordisk’s business interests, including because disclosure of any individual piece(s) of information could result in public identification of confidential materials. Novo Nordisk submits this information under CMS’s assurances of confidentiality (Guidance § 40.2.1 (citing id. § 40.2.2; 5 U.S.C. § 552(b)(3), (4); 18 U.S.C. § 1905))

and designates this submission as confidential and exempt from disclosure under Exemption 4 of the FOIA (45 C.F.R. 5.41). As such, predisclosure notification is required (45 C.F.R. 5.42). Novo Nordisk's future disclosure of any piece of the information contained herein and designated as confidential does not alter the status of the remaining information as exempt from disclosure or otherwise waive or forfeit Novo Nordisk's rights to confidential treatment and predisclosure notification.

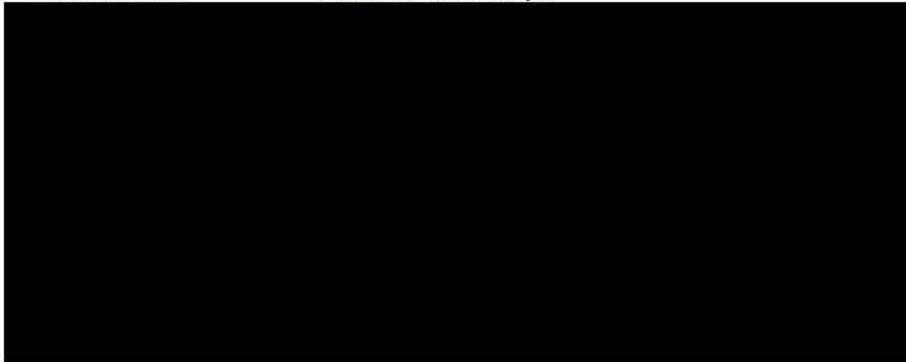
- b. Best Prices (BPs) are not reported for non-saleable or inapplicable NDCs, including samples. Also, Novo Nordisk is not reporting BP for the following NDC, which was launched on September 18, 2023, and for which we do not have data from which to calculate BP: 00169-3206-15). Finally, as explained further below, Novo Nordisk does not report BPs for NDCs of products repackaged by entities that do not qualify as "Secondary Manufacturers" under the ICR. See below for the list of NDCs for which Novo Nordisk is not reporting BPs.
- c. CMS's list of NDCs of selected drugs includes NDCs for unbranded biologic versions of Novo Nordisk products marketed by Novo Nordisk Pharma, Inc. (NNPI). NNPI qualifies as a "Secondary Manufacturer" under CMS's definitions in the ICR.



- e. Below is the list of NDCs for which Novo Nordisk is not reporting BP data:

NDC-11	Reason for Exclusion
00169200190	Diluent provided for no charge at physician request; akin to a sample
00169320190	Non-saleable sample
00169320490	Non-saleable inner NDC for non-saleable sample
00169320497	Non-saleable sample
00169320591	Non-saleable inner NDC for non-saleable sample
00169320595	Non-saleable sample
00169320611	No data to calculate BP

00169320615	No data to calculate BP
00169320691	Non-saleable inner NDC for non-saleable sample
00169320695	Non-saleable sample
00169330390	Non-saleable sample; discontinued
00169330391	Non-saleable sample; discontinued
00169633890	Non-saleable inner NDC for non-saleable sample; never launched
00169633897	Non-saleable sample; never launched
00169633990	Non-saleable inner NDC for non-saleable sample
00169633997	Non-saleable sample
00169633998	Non-saleable sample
00169750190	Non-saleable sample



- f. As required by the Medicaid Drug Rebate Program (MDRP) where two NDC-9s are the same dosage form and strength of the same drug, the BPs for the products are the lowest BP of the set. That is, BP is consistent across drugs of the same dosage form and strength.
- g. Question 18 requires reporting of quarterly “total unit volume,” which is defined as “the sum of monthly AMP units reported to the MDRP for the quarter.”
- h. The MDRP permits manufacturers up to three years from the date of initial submission to restate BP to reflect lagged information (e.g., rebates). Manufacturers regularly submit initial estimated BPs that are trued-up as necessary within that three year window. BPs

reported in response to Question 18 are the BPs certified in the MDRP system as of the date of submission of this data. As required in the ICR, the reported Medicaid BPs reflect any restatements that have been certified under the MDRP. The reported Medicaid BPs may be adjusted and restated in the future, subject to the three year restatement window specific to each quarter's submission. If BPs are restated, Novo Nordisk will notify CMS of the change in submitted BPs per the ICR's General Instructions.

G. Market Data and Revenue and Sales Volume Data					
Federal Supply Schedule Price					
<p>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.</p>					
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	00169-3201-11	2018-07-01 - 2018-12-31	\$150.15	ML	
Y	00169-3201-11	2019-01-01 - 2019-06-30	\$150.15	ML	
Y	00169-3201-11	2019-07-01 - 2019-12-31	\$165.01	ML	
Y	00169-3201-11	2020-01-01 - 2020-12-31	\$165.01	ML	
Y	00169-3201-11	2021-01-01 - 2021-12-31	\$165.01	ML	
Y	00169-3201-11	2022-01-01 - 2022-12-31	\$165.01	ML	

G. Market Data and Revenue and Sales Volume Data

Federal Supply Schedule Price

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

Federal Supply Schedule Price	National Drug Code (NDC-11)	Price Start Date to End Date	Federal Supply Schedule Service Price	Unit Type (EA, ML, GM)	Total Unit Volume
Y	00169-3201-11	2023-01-01 - 2023-06-30	\$165.01	ML	
Y	00169-3204-15	2018-07-01 - 2018-12-31	\$290.00	ML	
Y	00169-3204-15	2019-01-01 - 2019-06-30	\$290.00	ML	
Y	00169-3204-15	2019-07-01 - 2019-12-31	\$318.71	ML	
Y	00169-3204-15	2020-01-01 - 2020-12-31	\$318.71	ML	
Y	00169-3204-15	2021-01-01 - 2021-12-31	\$318.71	ML	
Y	00169-3204-15	2022-01-01 - 2022-12-31	\$318.71	ML	
Y	00169-3204-15	2023-01-01 - 2023-06-30	\$318.71	ML	
Y	00169-3205-15	2020-01-01 - 2020-12-31	\$336.88	ML	
Y	00169-3205-15	2021-01-01 - 2021-12-31	\$336.88	ML	

G. Market Data and Revenue and Sales Volume Data

Federal Supply Schedule Price

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

Federal Supply Schedule Price	National Drug Code (NDC-11)	Price Start Date to End Date	Federal Supply Schedule Service Price	Unit Type (EA, ML, GM)	Total Unit Volume
Y	00169-3205-15	2022-01-01 - 2022-12-31	\$336.88	ML	
Y	00169-3205-15	2023-01-01 - 2023-06-30	\$336.88	ML	
Y	00169-3303-12	2018-07-01 - 2018-12-31	\$224.55	ML	
Y	00169-3303-12	2019-01-01 - 2019-06-30	\$239.43	ML	
Y	00169-3303-12	2019-07-01 - 2019-12-31	\$263.12	ML	
Y	00169-3303-12	2020-01-01 - 2020-12-31	\$263.12	ML	
Y	00169-3303-12	2021-01-01 - 2021-12-31	\$263.12	ML	
Y	00169-3303-12	2022-01-01 - 2022-12-31	\$263.12	ML	
Y	00169-3303-12	2023-01-01 - 2023-06-30	\$263.12	ML	
Y	00169-6339-10	2018-07-01 - 2018-12-31	\$148.19	ML	

G. Market Data and Revenue and Sales Volume Data

Federal Supply Schedule Price

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

Federal Supply Schedule Price	National Drug Code (NDC-11)	Price Start Date to End Date	Federal Supply Schedule Service Price	Unit Type (EA, ML, GM)	Total Unit Volume
Y	00169-6339-10	2019-01-01 - 2019-06-30	\$158.00	ML	
Y	00169-6339-10	2019-07-01 - 2019-08-31	\$173.66	ML	
Y	00169-6339-10	2019-09-01 - 2019-12-31	\$173.64	ML	
Y	00169-6339-10	2020-01-01 - 2020-12-31	\$173.64	ML	
Y	00169-6339-10	2021-01-01 - 2021-12-31	\$173.64	ML	
Y	00169-6339-10	2022-01-01 - 2022-12-31	\$173.64	ML	
Y	00169-6339-10	2023-01-01 - 2023-06-30	\$173.64	ML	
Y	00169-7501-11	2018-07-01 - 2018-12-31	\$82.08	ML	
Y	00169-7501-11	2019-01-01 - 2019-06-30	\$87.52	ML	
Y	00169-7501-11	2019-07-01 - 2019-12-31	\$96.17	ML	

G. Market Data and Revenue and Sales Volume Data

Federal Supply Schedule Price

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

Federal Supply Schedule Price	National Drug Code (NDC-11)	Price Start Date to End Date	Federal Supply Schedule Service Price	Unit Type (EA, ML, GM)	Total Unit Volume
Y	00169-7501-11	2020-01-01 - 2020-12-31	\$96.17	ML	
Y	00169-7501-11	2021-01-01 - 2021-12-31	\$96.17	ML	
Y	00169-7501-11	2022-01-01 - 2022-12-31	\$96.17	ML	
Y	00169-7501-11	2023-01-01 - 2023-06-30	\$96.17	ML	
Y	73070-0100-11	2020-06-03 - 2020-12-31	\$107.87	ML	
Y	73070-0100-11	2021-01-01 - 2021-12-31	\$108.19	ML	
Y	73070-0100-11	2022-01-01 - 2022-12-31	\$108.06	ML	
Y	73070-0100-11	2023-01-01 - 2023-06-30	\$107.92	ML	
Y	73070-0102-15	2020-06-03 - 2020-12-31	\$200.06	ML	
Y	73070-0102-15	2021-01-01 - 2021-12-31	\$200.86	ML	

G. Market Data and Revenue and Sales Volume Data

Federal Supply Schedule Price

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

Federal Supply Schedule Price	National Drug Code (NDC-11)	Price Start Date to End Date	Federal Supply Schedule Service Price	Unit Type (EA, ML, GM)	Total Unit Volume
Y	73070-0102-15	2022-01-01 - 2022-12-31	\$201.07	ML	
Y	73070-0102-15	2023-01-01 - 2023-06-30	\$201.01	ML	
Y	73070-0103-15	2020-06-03 - 2020-12-31	\$207.74	ML	
Y	73070-0103-15	2021-01-01 - 2021-12-31	\$208.80	ML	
Y	73070-0103-15	2022-01-01 - 2022-12-31	\$208.54	ML	
Y	73070-0103-15	2023-01-01 - 2023-06-30	\$208.21	ML	

Explanations: Section G, Question 21: Explanation of Information Reported in Question 20: Federal Supply Schedule Price (794 words of 1,000 permitted)

- a. This response contains trade secret and confidential commercial and financial information that Novo Nordisk customarily and actually treats as private. Disclosure of this information would result in harm to Novo Nordisk’s business interests, including because disclosure of any individual piece(s) of information could result in public identification of confidential materials. Novo Nordisk submits this information under CMS’s assurances of confidentiality (Guidance § 40.2.1 (citing id. § 40.2.2; 5 U.S.C. § 552(b)(3), (4); 18 U.S.C. § 1905)) and designates this submission as confidential and exempt from disclosure under Exemption 4 of the FOIA (45 C.F.R. 5.41). As such,

predisdisclosure notification is required (45 C.F.R. 5.42). Novo Nordisk's future disclosure of any piece of the information contained herein and designated as confidential does not alter the status of the remaining information as exempt from disclosure or otherwise waive or forfeit Novo Nordisk's rights to confidential treatment and predisdisclosure notification.

- b. Novo Nordisk's list of non-reportable NDCs, as presented in response to Question 17 above, is adopted and incorporated herein by reference. FSS prices are not reported for non-saleable or inapplicable NDC-11s, including inner packages, samples, [REDACTED]

[REDACTED] In addition, Novo Nordisk is not reporting FSS for the following NDC, which was launched on September 18, 2023: 00169-3206-15). Finally, as explained further below, Novo Nordisk does not report FSS prices for NDCs of products repackaged by entities that do not qualify as "Secondary Manufacturers" under the ICR.

- c. CMS's list of NDCs of selected drugs includes NDCs for unbranded biologic versions of Novo Nordisk products marketed by Novo Nordisk Pharma, Inc. (NNPI). NNPI qualifies as a "Secondary Manufacturer" under CMS's definition as set forth in the ICR.

- e. NNPI is a single pricer. Therefore, FSS and Big Four prices for NNPI NDCs will be the same.
- f. Novo Nordisk Inc. (NNI) is a dual pricer. Therefore, FSS and Big Four pricing for its NDCs may be different.
- g. FSS prices reported in response to Question 20 include the Industrial Funding Fee (IFF) embedded in the prices. The prices provided thus match those presented in the VA National Acquisition Center database, as required by the ICR instructions.
- h. Prices on the VA National Acquisition Center database do not go back a full five years. The ICR requires that Novo Nordisk report the FSS/Big Four price information "that can be found online in the pharmaceutical pricing data for all VA National Acquisition Center programs." The VA makes only the current year FSS and Big Four prices available on the NAC website. Nevertheless, Novo Nordisk is providing FSS and Big Four pricing for the last five years, as Questions 20 and 22 seem to require.

- i. The ICR requires Novo Nordisk to report as “Total unit volume” in response to Question 20 “the total number of units (i.e., EA, ML, or GM) for each NDC-11 sold to direct federal purchasers” (emphasis added).

[Redacted]

G. Market Data and Revenue and Sales Volume Data					
Big Four Price					
Description: The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Big Four price of the selected drug. The Big Four price information reflects the information that can be found online in the pharmaceutical pricing data for all VA National Acquisition Center programs.					
Big Four Price	National Drug Code (NDC-11)	Price Start Date to End Date	Big Four Price	Unit Type (EA, ML, GM)	Total Unit Volume
Y	00169-3201-11	2018-07-01 - 2018-12-31	\$150.15	ML	[Redacted]
Y	00169-3201-11	2019-01-01 - 2019-06-30	\$150.15	ML	[Redacted]
Y	00169-3201-11	2019-07-01 - 2019-12-31	\$165.01	ML	[Redacted]
Y	00169-3201-11	2020-01-01 - 2020-12-31	\$165.01	ML	[Redacted]
Y	00169-3201-11	2021-01-01 - 2021-12-31	\$165.01	ML	[Redacted]
Y	00169-3201-11	2022-01-01 - 2022-12-31	\$165.01	ML	[Redacted]
Y	00169-3201-11	2023-01-01 - 2023-06-30	\$165.01	ML	[Redacted]
Y	00169-3204-15	2018-07-01 - 2018-12-31	\$290.00	ML	[Redacted]

G. Market Data and Revenue and Sales Volume Data

Big Four Price

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

Big Four Price	National Drug Code (NDC-11)	Price Start Date to End Date	Big Four Price	Unit Type (EA, ML, GM)	Total Unit Volume
Y	00169-3204-15	2019-01-01 - 2019-06-30	\$290.00	ML	
Y	00169-3204-15	2019-07-01 - 2019-12-31	\$318.71	ML	
Y	00169-3204-15	2020-01-01 - 2020-12-31	\$318.71	ML	
Y	00169-3204-15	2021-01-01 - 2021-12-31	\$318.71	ML	
Y	00169-3204-15	2022-01-01 - 2022-12-31	\$318.71	ML	
Y	00169-3204-15	2023-01-01 - 2023-06-30	\$318.71	ML	
Y	00169-3205-15	2020-01-01 - 2020-12-31	\$336.88	ML	
Y	00169-3205-15	2021-01-01 - 2021-12-31	\$336.88	ML	
Y	00169-3205-15	2022-01-01 - 2022-12-31	\$336.88	ML	
Y	00169-3205-15	2023-01-01 - 2023-06-30	\$336.88	ML	
Y	00169-3303-12	2018-07-01 - 2018-12-31	\$224.55	ML	

G. Market Data and Revenue and Sales Volume Data

Big Four Price

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

Big Four Price	National Drug Code (NDC-11)	Price Start Date to End Date	Big Four Price	Unit Type (EA, ML, GM)	Total Unit Volume
Y	00169-3303-12	2019-01-01 - 2019-06-30	\$239.43	ML	
Y	00169-3303-12	2019-07-01 - 2019-12-31	\$263.12	ML	
Y	00169-3303-12	2020-01-01 - 2020-12-31	\$263.12	ML	
Y	00169-3303-12	2021-01-01 - 2021-12-31	\$263.12	ML	
Y	00169-3303-12	2022-01-01 - 2022-12-31	\$263.12	ML	
Y	00169-3303-12	2023-01-01 - 2023-06-30	\$263.12	ML	
Y	00169-6339-10	2018-07-01 - 2018-12-31	\$148.19	ML	
Y	00169-6339-10	2019-01-01 - 2019-06-30	\$158.00	ML	
Y	00169-6339-10	2019-07-01 - 2019-08-31	\$173.66	ML	
Y	00169-6339-10	2019-09-01 - 2019-12-31	\$173.64	ML	
Y	00169-6339-10	2020-01-01 - 2020-12-31	\$173.64	ML	

G. Market Data and Revenue and Sales Volume Data

Big Four Price

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

Big Four Price	National Drug Code (NDC-11)	Price Start Date to End Date	Big Four Price	Unit Type (EA, ML, GM)	Total Unit Volume
Y	00169-6339-10	2021-01-01 - 2021-12-31	\$173.64	ML	
Y	00169-6339-10	2022-01-01 - 2022-12-31	\$173.64	ML	
Y	00169-6339-10	2023-01-01 - 2023-06-30	\$173.64	ML	
Y	00169-7501-11	2018-07-01 - 2018-12-31	\$82.08	ML	
Y	00169-7501-11	2019-01-01 - 2019-06-30	\$87.52	ML	
Y	00169-7501-11	2019-07-01 - 2019-12-31	\$96.17	ML	
Y	00169-7501-11	2020-01-01 - 2020-12-31	\$96.17	ML	
Y	00169-7501-11	2021-01-01 - 2021-12-31	\$96.17	ML	
Y	00169-7501-11	2022-01-01 - 2022-12-31	\$96.17	ML	
Y	00169-7501-11	2023-01-01 - 2023-06-30	\$96.17	ML	
Y	73070-0100-11	2020-06-03 - 2020-12-31	\$107.87	ML	

G. Market Data and Revenue and Sales Volume Data

Big Four Price

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

Big Four Price	National Drug Code (NDC-11)	Price Start Date to End Date	Big Four Price	Unit Type (EA, ML, GM)	Total Unit Volume
Y	73070-0100-11	2021-01-01 - 2021-12-31	\$108.19	ML	
Y	73070-0100-11	2022-01-01 - 2022-12-31	\$108.06	ML	
Y	73070-0100-11	2023-01-01 - 2023-06-30	\$107.92	ML	
Y	73070-0102-15	2020-06-03 - 2020-12-31	\$200.06	ML	
Y	73070-0102-15	2021-01-01 - 2021-12-31	\$200.86	ML	
Y	73070-0102-15	2022-01-01 - 2022-12-31	\$201.07	ML	
Y	73070-0102-15	2023-01-01 - 2023-06-30	\$201.01	ML	
Y	73070-0103-15	2020-06-03 - 2020-12-31	\$207.74	ML	
Y	73070-0103-15	2021-01-01 - 2021-12-31	\$208.80	ML	
Y	73070-0103-15	2022-01-01 - 2022-12-31	\$208.54	ML	
Y	73070-0103-15	2023-01-01 - 2023-06-30	\$208.21	ML	

Explanations: Section G, Question 23: Explanation of Information Reported in Response to Question 22: Big Four Price (799 of 1,000 words permitted)

- a. This response contains trade secret and confidential commercial and financial information that Novo Nordisk customarily and actually treats as private. Disclosure of this information would result in harm to Novo Nordisk’s business interests, including because disclosure of any individual piece(s) of information could result in public identification of confidential materials. Novo Nordisk submits this information under CMS’s assurances of confidentiality (Guidance § 40.2.1 (citing id. § 40.2.2; 5 U.S.C. § 552(b)(3), (4); 18 U.S.C. § 1905)) and designates this submission as confidential and exempt from disclosure under Exemption 4 of the FOIA (45 C.F.R. 5.41). As such, predisclosure notification is required (45 C.F.R. 5.42). Novo Nordisk’s future disclosure of any piece of the information contained herein and designated as confidential does not alter the status of the remaining information as exempt from disclosure or otherwise waive or forfeit Novo Nordisk’s rights to confidential treatment and predisclosure notification.
- b. Novo Nordisk’s list of non-reportable NDCs, as presented in response to Question 17 above, is adopted and incorporated herein by reference. Big Four Prices are not reported for non-saleable or inapplicable NDC-11s, including inner packages, samples, [REDACTED]

[REDACTED] In addition, Novo Nordisk is not reporting a Big Four price for the following NDC, which was launched on September 18, 2023: 00169-3206-15). Finally, as explained further below, Novo Nordisk does not report Non-FAMPs for NDCs of products repackaged by entities that do not qualify as “Secondary Manufacturers” under the ICR.



- d. NNPI is a single pricer. Therefore, FSS and Big Four prices for NNPI NDCs will be the same.
- e. Novo Nordisk Inc. (NNI) is a dual pricer. Therefore, FSS and Big Four pricing for its NDCs may be different.

- f. Big Four prices reported in response to Question 20 include the Industrial Funding Fee (IFF) embedded in the prices. The prices provided thus match those presented in the VA National Acquisition Center database, as required by the ICR instructions.
- g. Prices on the VA National Acquisition Center database do not go back a full five years. The ICR requires that Novo Nordisk report the FSS/Big Four price information “that can be found online in the pharmaceutical pricing data for all VA National Acquisition Center programs.” The VA makes only the current year FSS and Big Four prices available on the NAC website. Nevertheless, Novo Nordisk is providing FSS and Big Four pricing for the last five years, as Questions 20 and 22 seem to require.
- h. The ICR requires Novo Nordisk to report as “Total unit volume” in response to Question 22 “the total number of units (i.e., EA, ML, or GM) for each NDC-11 sold to the Big Four federal agencies (Department of Veterans Affairs, Department of Defense, the Public Health Service, and the Coast Guard).”



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
00169-3303-12	2018-Q1				ML	
00169-3303-12	2018-Q2				ML	
00169-3303-12	2018-Q3				ML	
00169-3303-12	2018-Q4				ML	
00169-3303-12	2019-Q1				ML	
00169-3303-12	2019-Q2				ML	
00169-3303-12	2019-Q3				ML	

G. Market Data and Revenue and Sales Volume Data

U.S. Commercial Average Net Unit Price

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

National Drug Code (NDC-11)	Quarter	U.S. Commercial Average Unit Net Price	U.S. Commercial Average Net Unit Price - Without Patient Assistance Programs	U.S. Commercial Average Net Unit Price- Best	Unit type (EA, ML, GM)	Total Unit Volume
00169-3303-12	2019-Q4				ML	
00169-3303-12	2020-Q1				ML	
00169-3303-12	2020-Q2				ML	
00169-3303-12	2020-Q3				ML	
00169-3303-12	2020-Q4				ML	
00169-3303-12	2021-Q1				ML	
00169-3303-12	2021-Q2				ML	
00169-3303-12	2021-Q3				ML	
00169-3303-12	2021-Q4				ML	
00169-3303-12	2022-Q1				ML	
00169-3303-12	2022-Q2				ML	
00169-3303-12	2022-Q3				ML	
00169-3303-12	2022-Q4				ML	
00169-6339-10	2018-Q1				ML	
00169-6339-10	2018-Q2				ML	
00169-6339-10	2018-Q3				ML	
00169-6339-10	2018-Q4				ML	
00169-6339-10	2019-Q1				ML	
00169-6339-10	2019-Q2				ML	
00169-6339-10	2019-Q3				ML	

G. Market Data and Revenue and Sales Volume Data

U.S. Commercial Average Net Unit Price

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

National Drug Code (NDC-11)	Quarter	U.S. Commercial Average Unit Net Price	U.S. Commercial Average Net Unit Price - Without Patient Assistance Programs	U.S. Commercial Average Net Unit Price- Best	Unit type (EA, ML, GM)	Total Unit Volume
00169-6339-10	2019-Q4				ML	
00169-6339-10	2020-Q1				ML	
00169-6339-10	2020-Q2				ML	
00169-6339-10	2020-Q3				ML	
00169-6339-10	2020-Q4				ML	
00169-6339-10	2021-Q1				ML	
00169-6339-10	2021-Q2				ML	
00169-6339-10	2021-Q3				ML	
00169-6339-10	2021-Q4				ML	
00169-6339-10	2022-Q1				ML	
00169-6339-10	2022-Q2				ML	
00169-6339-10	2022-Q3				ML	
00169-6339-10	2022-Q4				ML	
00169-7501-11	2018-Q1				ML	
00169-7501-11	2018-Q2				ML	
00169-7501-11	2018-Q3				ML	
00169-7501-11	2018-Q4				ML	
00169-7501-11	2019-Q1				ML	
00169-7501-11	2019-Q2				ML	
00169-7501-11	2019-Q3				ML	

G. Market Data and Revenue and Sales Volume Data

U.S. Commercial Average Net Unit Price

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

National Drug Code (NDC-11)	Quarter	U.S. Commercial Average Unit Net Price	U.S. Commercial Average Net Unit Price - Without Patient Assistance Programs	U.S. Commercial Average Net Unit Price- Best	Unit type (EA, ML, GM)	Total Unit Volume
00169-7501-11	2019-Q4				ML	
00169-7501-11	2020-Q1				ML	
00169-7501-11	2020-Q2				ML	
00169-7501-11	2020-Q3				ML	
00169-7501-11	2020-Q4				ML	
00169-7501-11	2021-Q1				ML	
00169-7501-11	2021-Q2				ML	
00169-7501-11	2021-Q3				ML	
00169-7501-11	2021-Q4				ML	
00169-7501-11	2022-Q1				ML	
00169-7501-11	2022-Q2				ML	
00169-7501-11	2022-Q3				ML	
00169-7501-11	2022-Q4				ML	
00169-3201-11	2018-Q1				ML	
00169-3201-11	2018-Q2				ML	
00169-3201-11	2018-Q3				ML	
00169-3201-11	2018-Q4				ML	
00169-3201-11	2019-Q1				ML	
00169-3201-11	2019-Q2				ML	
00169-3201-11	2019-Q3				ML	

G. Market Data and Revenue and Sales Volume Data

U.S. Commercial Average Net Unit Price

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

National Drug Code (NDC-11)	Quarter	U.S. Commercial Average Unit Net Price	U.S. Commercial Average Net Unit Price - Without Patient Assistance Programs	U.S. Commercial Average Net Unit Price- Best	Unit type (EA, ML, GM)	Total Unit Volume
00169-3201-11	2019-Q4				ML	
00169-3201-11	2020-Q1				ML	
00169-3201-11	2020-Q2				ML	
00169-3201-11	2020-Q3				ML	
00169-3201-11	2020-Q4				ML	
00169-3201-11	2021-Q1				ML	
00169-3201-11	2021-Q2				ML	
00169-3201-11	2021-Q3				ML	
00169-3201-11	2021-Q4				ML	
00169-3201-11	2022-Q1				ML	
00169-3201-11	2022-Q2				ML	
00169-3201-11	2022-Q3				ML	
00169-3201-11	2022-Q4				ML	
00169-3204-15	2018-Q1				ML	
00169-3204-15	2018-Q2				ML	
00169-3204-15	2018-Q3				ML	
00169-3204-15	2018-Q4				ML	
00169-3204-15	2019-Q1				ML	
00169-3204-15	2019-Q2				ML	
00169-3204-15	2019-Q3				ML	

G. Market Data and Revenue and Sales Volume Data

U.S. Commercial Average Net Unit Price

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

National Drug Code (NDC-11)	Quarter	U.S. Commercial Average Unit Net Price	U.S. Commercial Average Net Unit Price - Without Patient Assistance Programs	U.S. Commercial Average Net Unit Price- Best	Unit type (EA, ML, GM)	Total Unit Volume
00169-3204-15	2019-Q4				ML	
00169-3204-15	2020-Q1				ML	
00169-3204-15	2020-Q2				ML	
00169-3204-15	2020-Q3				ML	
00169-3204-15	2020-Q4				ML	
00169-3204-15	2021-Q1				ML	
00169-3204-15	2021-Q2				ML	
00169-3204-15	2021-Q3				ML	
00169-3204-15	2021-Q4				ML	
00169-3204-15	2022-Q1				ML	
00169-3204-15	2022-Q2				ML	
00169-3204-15	2022-Q3				ML	
00169-3204-15	2022-Q4				ML	
00169-3205-15	2019-Q4				ML	
00169-3205-15	2020-Q1				ML	
00169-3205-15	2020-Q2				ML	
00169-3205-15	2020-Q3				ML	
00169-3205-15	2020-Q4				ML	
00169-3205-15	2021-Q1				ML	
00169-3205-15	2021-Q2				ML	

G. Market Data and Revenue and Sales Volume Data

U.S. Commercial Average Net Unit Price

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

National Drug Code (NDC-11)	Quarter	U.S. Commercial Average Unit Net Price	U.S. Commercial Average Net Unit Price - Without Patient Assistance Programs	U.S. Commercial Average Net Unit Price- Best	Unit type (EA, ML, GM)	Total Unit Volume
00169-3205-15	2021-Q3				ML	
00169-3205-15	2021-Q4				ML	
00169-3205-15	2022-Q1				ML	
00169-3205-15	2022-Q2				ML	
00169-3205-15	2022-Q3				ML	
00169-3205-15	2022-Q4				ML	
73070-0100-11	2020-Q1				ML	
73070-0100-11	2020-Q2				ML	
73070-0100-11	2020-Q3				ML	
73070-0100-11	2020-Q4				ML	
73070-0100-11	2021-Q1				ML	
73070-0100-11	2021-Q2				ML	
73070-0100-11	2021-Q3				ML	
73070-0100-11	2021-Q4				ML	
73070-0100-11	2022-Q1				ML	
73070-0100-11	2022-Q2				ML	
73070-0100-11	2022-Q3				ML	
73070-0100-11	2022-Q4				ML	
73070-0102-15	2020-Q1				ML	
73070-0102-15	2020-Q2				ML	

G. Market Data and Revenue and Sales Volume Data

U.S. Commercial Average Net Unit Price

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

National Drug Code (NDC-11)	Quarter	U.S. Commercial Average Unit Net Price	U.S. Commercial Average Net Unit Price - Without Patient Assistance Programs	U.S. Commercial Average Net Unit Price- Best	Unit type (EA, ML, GM)	Total Unit Volume
73070-0102-15	2020-Q3				ML	
73070-0102-15	2020-Q4				ML	
73070-0102-15	2021-Q1				ML	
73070-0102-15	2021-Q2				ML	
73070-0102-15	2021-Q3				ML	
73070-0102-15	2021-Q4				ML	
73070-0102-15	2022-Q1				ML	
73070-0102-15	2022-Q2				ML	
73070-0102-15	2022-Q3				ML	
73070-0102-15	2022-Q4				ML	
73070-0103-15	2020-Q1				ML	
73070-0103-15	2020-Q2				ML	
73070-0103-15	2020-Q3				ML	
73070-0103-15	2020-Q4				ML	
73070-0103-15	2021-Q1				ML	
73070-0103-15	2021-Q2				ML	
73070-0103-15	2021-Q3				ML	
73070-0103-15	2021-Q4				ML	
73070-0103-15	2022-Q1				ML	
73070-0103-15	2022-Q2				ML	

G. Market Data and Revenue and Sales Volume Data

U.S. Commercial Average Net Unit Price

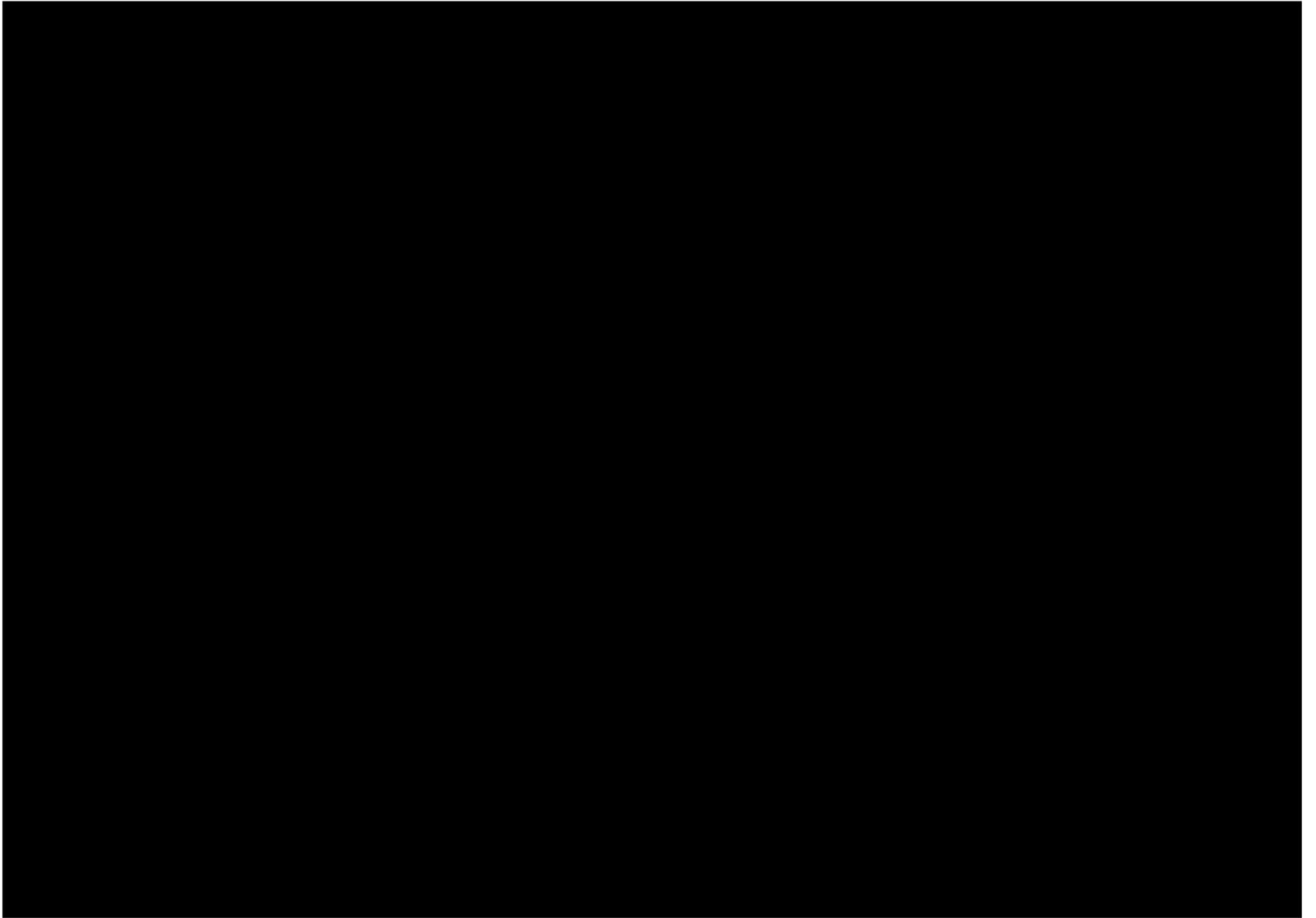
Description: The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides the U.S. commercial average net unit price, including group and individual commercial plans on- and off-exchange of the selected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

National Drug Code (NDC-11)	Quarter	U.S. Commercial Average Unit Net Price	U.S. Commercial Average Net Unit Price - Without Patient Assistance Programs	U.S. Commercial Average Net Unit Price- Best	Unit type (EA, ML, GM)	Total Unit Volume
73070-0103-15	2022-Q3				ML	
73070-0103-15	2022-Q4				ML	

Explanations:

- a. This response contains trade secret and confidential commercial and financial information that Novo Nordisk customarily and actually treats as private. Disclosure of this information would result in harm to Novo Nordisk’s business interests, including because disclosure of any individual piece(s) of information could result in public identification of confidential materials. Novo Nordisk submits this information under CMS’s assurances of confidentiality (Guidance § 40.2.1 (citing id. § 40.2.2; 5 U.S.C. § 552(b)(3), (4); 18 U.S.C. § 1905)) and designates this submission as confidential and exempt from disclosure under Exemption 4 of the FOIA (45 C.F.R. 5.41). As such, predisclosure notification is required (45 C.F.R. 5.42). Novo Nordisk’s future disclosure of any piece of the information contained herein and designated as confidential does not alter the status of the remaining information as exempt from disclosure or otherwise waive or forfeit Novo Nordisk’s rights to confidential treatment and predisclosure notification.
- b. Novo Nordisk’s list of non-reportable NDCs, as presented in response to Question 17 above, is adopted and incorporated herein by reference. In addition, Novo Nordisk is not reporting U.S. Commercial Average Net Unit Prices (CANUPs) for the following NDC, which was launched on September 14, 2023, and for which we do not have data from which to calculate CANUPs: 00169-3206-15). [REDACTED]

[REDACTED]





Manufacturer E2 Submission – Novo Nordisk, Inc.



Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	INSULIN ASPART, HUMAN
	Respondent Name	[REDACTED]
	Organization Name (if applicable)	Novo Nordisk Inc
	Respondent Email	[REDACTED]
	Who is completing this form?	[REDACTED]
Question 27: Prescribing Information	Prescribing Information	<p>[REDACTED]</p> <p>For clarity purposes, Novo Nordisk provides its responses to Section I, “Evidence About Selected Drugs and Their Therapeutic Alternatives Form,” including this response, as a complete PDF document. This was uploaded within “Additional Materials for Questions 28”.</p> <p>Novo Nordisk Inc. is providing this summary of information in response to an unsolicited inquiry by CMS. Please see cited references for full discussion of study design and results.</p> <p>1. Disease Background - Information About Type 1 and Type 2 Diabetes</p> <p>Diabetes is one of the most prevalent diseases in the United States (U.S.), with 11.3% of people of all ages and 29.2% of adults aged 65 or older currently living with the disease. The Centers for Disease Control and Prevention (CDC) reports that in 2019, 37.1 million Americans had diabetes, with 15.9 million of them aged 65 years or older. Of the 37.1 million Americans with diabetes, 90-95% (33.4 - 35.2 million) are living with type 2 diabetes (T2D) with the remaining 5-10% (1.9 - 3.7 million) suffer from type 1 diabetes (T1D).</p> <p>Diabetes affects how the body turns food into energy (CDC). In healthy individuals, beta cells (b-cells) in the pancreas release the hormone insulin with each meal to help the body use and/or store the blood glucose (blood sugar) released from digestion of food. For patients with diabetes, the body doesn’t make enough insulin and/or doesn’t respond to insulin as effectively. Individuals diagnosed with diabetes are either diagnosed with T1D where the pancreas no longer makes insulin or T2D where the body suffers from a combination of inadequate insulin secretion, insulin resistance, and metabolic syndrome.</p> <p>The absence of insulin production or secretion leads to excess blood sugar staying within the blood. Over time, if diabetes is not properly controlled it can lead to several macrovascular and microvascular complications. The potential microvascular complications include retinopathy causing vision impairment and blindness, nephropathy causing loss of kidney function, and neuropathy causing peripheral nerve damage that can manifest in many ways including loss of limbs and sexual dysfunction. The potential macrovascular complications include cardiovascular</p>



Question	Sub-Question	Response
		<p>disease such as myocardial infarction, stroke, and ischemic disease (Fowler, Michael J. "Microvascular and Macrovascular Complications of Diabetes." Clinical Diabetes, vol. 26, no. 2, 2008, pp. 77–82)</p> <p>Since insulin production is either completely lost or critically reduced for patients with T1D, insulin replacement therapy is an absolute requirement. Additionally, it is important to note that individuals living with T2D suffer from a progressive disease and these individuals also eventually require insulin therapy to maintain normal glucose levels. To address the unmet needs of patients requiring insulin therapy, innovation of commercially available insulin products has been necessary since its initial discovery. Before insulin was discovered in 1921, those with T1D died within weeks to years of its onset. The only available treatment was a starvation diet. Bovine and porcine derived insulins were the first commercially available insulin therapy, starting in 1923. However, these first insulin formulations were short acting, requiring patients to take frequent injections, often in the middle of the night, which increases the risk of missing doses. To respond to the unmet need of fewer daily injections, researchers and founders of Novo Nordisk Inc., as well as research teams from Toronto, identified ways to lengthen insulin’s duration of action by the mid-1930’s. Treatment that avoided the frequent allergic reactions associated with bovine and porcine insulins remained an unmet need until the development of synthetic human insulin in 1978, which became commercially available in 1982.</p> <p>While synthetic human insulins represented a major development, the need remained for therapies with characteristics that would better imitate the mealtime response of a normal functioning pancreas to mitigate glucose spikes whenever a patient ate a meal. This need led to years of research and the development of faster-acting insulins that keep glucose levels closer to normal around meals. The first of these rapid-acting insulins became broadly available to patients in 1996. Since then, research has continued to further respond to patient needs with multiple innovations achieved, including ultra-rapid acting insulins, which work even faster to better replicate the natural pancreatic insulin response when eating a meal while providing more dosing flexibility to patients compared to previous insulins. Additional innovations include improvements in the insulin delivery systems with the advent of pens which provide an easier and more accurate method of administration, in addition to being less painful, and are more discreet compared with vials and syringes. Substantial evidence demonstrates that insulin pen devices have the potential to improve adherence, enhance quality of life, and reduce the risk of hyperglycemia (Magwire, Melissa L. “Addressing Barriers to Insulin Therapy: The Role of Insulin Pens.” American Journal of Therapeutics, vol. 18, no. 5, 2011, pp. 392-402).</p> <p>2. Indications for NovoLog® and FIASP®</p> <p>a. NovoLog®</p> <p>Approved in 2000, NovoLog® is a rapid-acting insulin analog containing insulin aspart utilized to improve glycemic control in adults and children with type 1 and T2D (NovoLog® Package Insert). In lay terms, rapid-acting insulins imitate the body’s secretion of insulin after a meal, preventing blood sugar spikes that can result in the immediate symptoms of thirst, fatigue, nausea, and blurred vision – and over time cause the serious and long term microvascular and macrovascular complications mentioned earlier. NovoLog® is available as a subcutaneous</p>



Question	Sub-Question	Response
		<p>injection, continuous subcutaneous infusion (via a pump), or for intravenous use and is available in multiple dosage forms and strengths, and in several different devices depending on a patient’s need. See Section 3 for more prescribing information.</p> <p>b. FIASP®</p> <p>Approved in 2017, FIASP® is a newer insulin formulation with an enhanced rapid-action profile due to a shorter time of onset (FIASP® Package Insert). FIASP® is an ultra-rapid acting insulin analog utilized to improve glycemic control in adults and children with T1D and T2D. FIASP® is a faster-acting insulin aspart due to the addition of vitamin B3 (niacinamide) to increase the speed of initial absorption and an amino acid (L-arginine) to stabilize the formulation. This results in faster absorption with differentiated dosing for use in T1D and T2D. FIASP® appears in the bloodstream faster than NovoLog®; while NovoLog® is approved for use within 5-10 minutes immediately before a meal, FIASP® is approved for use at the start or within 20 minutes after starting a meal. This dosing flexibility provides patients more leeway in their mealtime dosing and was shown to provide better post-prandial (post-meal) glycemic control when compared to NovoLog® in Phase 3 clinical trials.</p> <p>Failure to follow each product’s specific dosing instructions can increase the risk of hypoglycemia. See Section 3 for more prescribing information.</p> <p>3. Therapeutic Alternatives</p> <p>The ADA identifies three characteristics of insulins that differentiate them from one another:</p> <ul style="list-style-type: none"> • Onset of action: Length of time before insulin reaches blood stream and begins lowering blood glucose • Peak time: Time during which insulin is at maximum strength • Duration: Duration of time for which insulin continues to lower blood glucose <p>There are two main categories of insulin, based on use:</p> <ul style="list-style-type: none"> • Basal insulin - Basal insulins are designed to be injected once or twice daily to maintain insulin levels throughout the day and night. The objective of basal insulin is to keep blood sugar levels at goal when one is not eating – but it is not enough to cover glucose spikes after meals. • Prandial insulin - Prandial insulins have faster onsets and peaks, with shorter durations of action than basal insulins. They are taken around mealtimes to help keep glucose levels closer to normal for meals. <p>The prandial insulin category is further differentiated into the following sub-categories: short-acting, rapid-acting, and ultra-rapid acting insulins. Prior to addressing what may be appropriate therapeutic alternatives, it is important to note that research and guidelines support the fact that the short-acting insulin sub-category, also referred to as regular human insulin, is not an appropriate therapeutic alternative to NovoLog® or FIASP®. The ADA Standards of Care 2023 differentiate between short-acting and rapid-acting insulin when they state that patients with T1D should use rapid-acting insulin analogs as they are associated with less hypoglycemia and weight gain as well as lower HbA1c compared with short-acting (human insulins). The guidelines go on to state that the preferred injection insulin regimen for patients with T1D is a long-acting analog with flexible doses of either an ultra-rapid acting analog or rapid-acting analog at meals. Similarly, the American Association of Clinical Endocrinology (AACE) guidelines state</p>



Question	Sub-Question	Response
		<p>that ‘Rapid-acting insulin analogs are preferred over human insulin preparations (e.g., regular insulin) because of their comparatively earlier onset of action’, further underscoring the distinction between the two.</p> <p>a. Therapeutic Alternatives for NovoLog® The most “clinically comparable therapeutic alternative” to NovoLog® is Humalog (insulin lispro) and its follow-on biologic ADMELOG (insulin lispro). Humalog is indicated to improve glycemic control in children and adults with both T1D and T2D. ADMELOG is indicated to improve glycemic control in adults and children aged 3 years and older with T1D and adults with T2D. Prescribing information about NovoLog®, Humalog and ADMELOG is summarized below. Refer to the package inserts for additional information. Summary of Prescribing Information for NovoLog® and its Therapeutic Alternatives Selected Drug: <ul style="list-style-type: none"> • NovoLog® (Insulin aspart) (Novo Nordisk, Inc.) Therapeutic Alternatives: <ul style="list-style-type: none"> • Humalog (Insulin lispro) (Eli Lilly and Company) • ADMELOG (Insulin lispro) (Sanofi-Aventis LLC) Speed of onset/Insulin Type: <ul style="list-style-type: none"> • NovoLog®: Rapid-acting • Humalog: Rapid-acting • ADMELOG: Rapid-acting Administration: <ul style="list-style-type: none"> • NovoLog®: SC injection, immediately (within 5-10 minutes) prior to the start of a meal, continuous SC infusion (use of insulin pump), intravenous infusion (after dilution and under medical supervision) • Humalog: SC injection, within 15 minutes before a meal or immediately after a meal, continuous SC infusion (use of insulin pump), intravenous infusion (HUMALOG U-100 only after dilution and under medical supervision) • ADMELOG: SC injection, within 15 minutes before a meal or immediately after a meal, continuous SC infusion (use of insulin pump), intravenous infusion (after dilution and under medical supervision) Indications: <ul style="list-style-type: none"> • NovoLog®: Improve glycemic control • Humalog: Improve glycemic control • ADMELOG: Improve glycemic control Dosage forms and strengths: <ul style="list-style-type: none"> • NovoLog®: Each presentation contains 100 Units of insulin aspart per mL (U-100), available in various devices including vials, PenFill® cartridges, FlexPen®, and FlexTouch® • Humalog: Injection available in 100 units/mL (U-100) in various devices including vials, KwikPen® prefilled pen, </p>



Question	Sub-Question	Response
		<p>Tempo Pen[®] prefilled pen, KwikPen[®] prefilled pen, and single-patient-use cartridges and 200 units/mL (U-200) available in KwikPen[®] prefilled pen</p> <ul style="list-style-type: none"> • ADMELOG: Injection available in 100 units/mL (U-100) in various devices including vials and SoloStar[®] prefilled pens <p>Populations:</p> <ul style="list-style-type: none"> • T1D: NovoLog[®] (Adults & Children), Humalog (Adults & Children), ADMELOG (Adults and Children 3 years and older) • T2D: NovoLog[®] (Adults & Children), Humalog (Adults & Children), ADMELOG (Adults) <p>b. Therapeutic Alternatives For FIASP[®]</p> <p>The most “clinically comparable therapeutic alternative” to FIASP[®] is Lyumjev (insulin lispro-aabc). Lyumjev is indicated to improve glycemic control in children and adults with T1D and T2D. Prescribing information about FIASP[®] and Lyumjev, is detailed below. Refer to the package inserts for additional information.</p> <p>Summary of Prescribing Information for FIASP[®] and its Therapeutic Alternatives</p> <p>Selected Drug</p> <ul style="list-style-type: none"> • FIASP[®] (Ultra-rapid acting insulin aspart) <p>Therapeutic Alternative:</p> <ul style="list-style-type: none"> • Lyumjev (Insulin lispro-aabc) (Eli Lilly and Company “LYUMJEV PI”) <p>Speed of onset/Insulin Type:</p> <ul style="list-style-type: none"> • FIASP: Faster rapid-acting • Lyumjev: Faster rapid-acting <p>Administration:</p> <ul style="list-style-type: none"> • FIASP[®]: Subcutaneous injection, start of a meal or within 20 minutes after starting a meal, continuous SC infusion (use of insulin pump), intravenous infusion (after dilution and under medical supervision) • Lyumjev: Subcutaneous injection, start of a meal or within 20 minutes after starting a meal, LYUMJEV U-100 only by use of insulin pump, intravenous infusion (LYUMJEV U-100 only after dilution and under medical supervision) <p>Indications:</p> <ul style="list-style-type: none"> o FIASP[®]: Improve glycemic control o Lyumjev: Improve glycemic control <p>Dosage forms and strengths:</p> <ul style="list-style-type: none"> • FIASP[®]: Injection available in 100 units/mL (U-100) and various formats, including multiple-dose vial, FIASP[®] FlexTouch[®] pen, PenFill[®] cartridges for use in a PenFill[®] cartridge device, and PumpCart[®] cartridges for use in a compatible insulin pump. • Lyumjev: Injection available in 100 units/mL (U-100) and various formats, including vial, KwikPen[®], Tempo Pen[®], and single-patient-use cartridges.



Question	Sub-Question	Response
		<p>Populations:</p> <ul style="list-style-type: none"> • T1D: <ul style="list-style-type: none"> o FIASP®: Adults & Children o Lyumjev: Adults & Children • T2D: <ul style="list-style-type: none"> o FIASP®: Adults & Children o Lyumjev: Adults & Children <p>4. Guideline Recommendations in Course of Care: NovoLog® and FIASP®</p> <p>a. Importance of Assessing Glycemic Control</p> <p>Glycemic control is assessed by HbA1c measurement, continuous glucose monitoring (CGM), and blood glucose monitoring (BGM). HbA1c is the metric used to date in clinical trials demonstrating the benefits of improved glycemic control. Individual glucose monitoring is a useful tool for diabetes self-management, which includes meals, physical activity, and medication adjustment, particularly in individuals taking insulin. According to 2023 ADA guidelines, HbA1c alone does not provide a measure of glycemic variability, fluctuations in blood glucose levels throughout the day, or hypoglycemia. For patients prone to glycemic variability, especially people with T1D or T2D with severe insulin deficiency, glycemic control is best evaluated by the combination of results from BGM and HbA1c measurement.</p> <p>b. T1D Treatment Guidelines Specific to Rapid-Acting Insulins</p> <p>The ADA Standards of Care recommend the use rapid-acting insulins (prandial insulins) in T1D as follows:</p> <ul style="list-style-type: none"> • “Most individuals with T1D should use rapid-acting insulin analogs to reduce hypoglycemia risk.” o Rapid-acting insulin analogs are associated with less hypoglycemia and weight gain as well as lower HbA1c compared with short-acting (human insulins). o Ultra-rapid acting insulins may reduce prandial excursions better than rapid-acting analogs. • “Most individuals with T1D should be treated with multiple daily injections of prandial and basal insulin, or continuous subcutaneous insulin infusion.” o The optimal time to administer prandial insulin varies, based on the pharmacokinetics of the formulation, the premeal blood glucose level, and carbohydrate consumption. o The preferred injection insulin regimen for patients with T1D is taking a long-acting analog with flexible doses of an ultra-rapid acting analog or rapid-acting analog at meals. <p>c. T2D Treatment Guidelines Specific to Rapid-Acting Insulins</p> <p>The ADA Standards of Care also recommend the use of rapid-acting insulins (prandial insulins) in T2D as an add-on to a GLP-1 RA to reach glycemic targets as follows:</p>



Question	Sub-Question	Response
		<ul style="list-style-type: none"> • “Many individuals with T2D require doses of insulin before meals, in addition to basal insulin, to reach glycemic targets.” • “If the individual is not already being treated with a GLP-1 RA, a GLP-1 RA (either in free combination or fixed-ratio combination) should be considered prior to prandial insulin...”. “For individuals who advance to prandial insulin, a prandial insulin dose of 4 units or 10% of the amount of basal insulin at the largest meal or the meal with the greatest post-prandial excursion is a safe estimate for initiating therapy. The prandial insulin regimen can then be intensified based on individual needs.” <p>d. Considerations for NovoLog® and FIASP® Based on Modes of Administration</p> <p>The 2023 ADA Standards of Care recognize the value of flexible modes of administration of rapid-acting insulins brought about by insulin pens and pumps and make the following recommendations:</p> <ul style="list-style-type: none"> • “For people with insulin-requiring diabetes on multiple daily injections, insulin pens are preferred [to syringes] in most cases”. • “Automated insulin delivery systems [including pumps] should be offered for diabetes management to youth and adults with T1D who are capable of using the device safely”. • Insulin pump therapy can be offered for diabetes management to youth and adults on multiple daily injections with T2D who are capable of using the device safely. <p>Innovation in prandial insulin and the ways in which it is administered have helped address many of the unmet needs for patients living with diabetes, such as post-prandial glucose control, overcoming restrictions on daily physical activities, and improvement in patient experience. An independent, online survey of adults with T1D, and parents and physicians of children with T1D found that 91% of adults and 97% of parents experienced at least one major challenge with mealtime insulin dosing (Fowler, Michael J. "Microvascular and Macrovascular Complications of Diabetes." Clinical Diabetes, vol. 26, no. 2, 2008, pp. 77–82.) Novo Nordisk Inc.’s responses to Questions 28-32 will demonstrate that the evolution of prandial insulin from short-acting (human) to rapid-acting to ultra-rapid acting has not only improved post-prandial glucose control in patients, but also helped address their disease burden through more flexible dosing and improved modes of administration.</p>
	Evidence Submitted include a cost-effectiveness measure?	N
	What type of Evidence is shown?	



Question	Sub-Question	Response
<p>Question 28: Therapeutic Impact and Comparative Effectiveness</p>	<p>Therapeutic Impact and Comparative Effectiveness</p>	<div style="background-color: black; height: 40px; width: 100%; margin-bottom: 10px;"></div> <p>For clarity purposes, Novo Nordisk provides its responses to Section I, “Evidence About Selected Drugs and Their Therapeutic Alternatives Form,” including this response, as a complete PDF document. This was uploaded within “Additional Materials for Questions 28”.</p> <p>Novo Nordisk Inc. is providing this summary of information in response to an unsolicited inquiry by CMS. Please see cited references for full discussion of study design and results.</p> <p>1. Description of Important Outcomes for Evaluating Insulin Treatments</p> <p>Accepted outcomes for evaluating insulins as a pharmacologic treatment for patients living with diabetes are as follows:</p> <p>a. Hemoglobin A1C</p> <p>The Hemoglobin A1c (HbA1c) measurement is an indicator of a patients’ average glucose control over the prior three months and whether their desired glycemic targets have been achieved. Change in HbA1c from baseline is the most common metric in clinical trials and other studies to demonstrate improved glycemic control [1].</p> <p>b. Post-Prandial Glucose</p> <p>Post-prandial glucose (PPG) measures the glucose level achieved at the time of testing after a meal is consumed. This is typically assessed one or two hours after the meal. Elevated PPG levels may be associated with adverse outcomes, and it is recommended that PPG levels be monitored in individuals when their pre-meal glucose values are within target range, but HbA1c values are above target [1].</p> <p>c. Safety (Hypoglycemia)</p> <p>The key safety concern associated with insulin injectables is hypoglycemia (low blood sugar). In general, patients with both type 1 diabetes (T1D) and type 2 diabetes (T2D) must ensure that they do not take more insulin than needed, which may cause hypoglycemia and in severe cases, can lead to unconsciousness, seizures, and brain function impairment [2]. Nocturnal hypoglycemia is a type of hypoglycemia that tends to occur if a patient does not eat enough food after taking an insulin dose or taking more insulin than prescribed in the evening [3].</p> <p>In the sections that follow, we will present effectiveness and safety data for NovoLog® and its therapeutic alternative Humalog. We will not present any data for ADMELOG, as it is a follow-on biologic of Humalog (same active ingredient - insulin lispro) and is expected to have the same effectiveness and safety profile. The safety and effectiveness of ADMELOG have been established in clinical studies in adult patients with T1D and T2D and is based on adequate and well controlled studies of ‘another insulin lispro product’ in adult and pediatric patients 3 years of age and older with T1D and adult patients with T2D [4].</p> <p>2. Clinical Outcomes of NovoLog®</p> <p>Key Takeaways</p> <ul style="list-style-type: none"> • The comparator group in Phase 3 clinical trial programs for rapid-acting NovoLog® and Humalog was regular



Question	Sub-Question	Response
		<p>human insulin, also referred to as short-acting, because it was the only prandial insulin available when these Phase 3 programs were designed.</p> <ul style="list-style-type: none"> • NovoLog[®] and Humalog Phase 3 clinical trials were structured to be treat-to-target, which means the overall HbA1c reductions are expected to be the same across treatment groups. • NovoLog[®] and Humalog were found to be non-inferior to regular human insulin on HbA1c and hypoglycemia outcomes in T1D and T2D. • NovoLog[®] is superior to regular human insulin on PPG levels achieved after mealtime in T1D patients. <p>The Phase 3 Clinical Trial programs for NovoLog[®] and Humalog used regular human insulin as their active comparator [2], [5]. For the NovoLog[®] clinical trial program, regular human insulin was chosen as the active comparator because it was the only prandial insulin available when the Phase 3 program was designed. Humalog was the first rapid-acting human insulin analog available on the market and did not receive FDA approval nor become commercially available until 1996, which was after the development and initial implementation of the NovoLog[®] Phase 3a clinical trial program.</p> <p>Note: There is no pivotal head-to-head trial comparing efficacy or safety of NovoLog[®] with Humalog, so no direct comparative effectiveness statements can be made from these studies.</p> <p>a. Effectiveness of NovoLog[®] and Humalog</p> <p>HbA1c</p> <p>As per U.S. Food and Drug Administration (FDA) directive, clinical development program for NovoLog[®] used non-inferiority for change in HbA1c as the primary endpoint [6]. It is important to note that due to FDA guidance the programs were designed as treat-to-target trials where insulin doses in both comparator and investigational arms are titrated to achieve a known and validated target level for glycemic control [6]. For this reason, overall HbA1c reductions in treat-to-target studies are expected to be the same among treatment groups, with no differences in efficacy expected [7].</p> <p>Table 1 summarizes HbA1c results for each product’s pivotal trials when administered as a subcutaneous daily injection [2], [5]. NovoLog[®] and Humalog were found to be non-inferior to regular human insulin on change in HbA1c in T1D and T2D.</p> <p>Two open-label, parallel design pivotal trials compared NovoLog[®] to buffered regular human insulin (Velosulin) in adults with T1D receiving a subcutaneous infusion with an external insulin pump. The two treatment regimens had comparable changes in HbA1c [2].</p> <p>Post-Prandial Glucose</p> <p>In the NovoLog[®] T1D pivotal trial, mean PPG levels (mg/dl ± SEM) were significantly lower for subjects in the NovoLog[®] group compared with the regular human insulin group after breakfast (156 ± 3.4 vs. 185 ± 4.7), lunch (137</p>



Question	Sub-Question	Response
		<p>± 3.1 vs. 162 ± 4.1), and dinner (153 ± 3.1 vs. 168 ± 4.1), when assessed after 6 months of treatment [8]. These data show that the patients taking NovoLog[®] did not experience significant spikes in their blood glucose readings after a meal compared to those taking regular human insulin.</p> <p>b. Safety of NovoLog[®] and Humalog</p> <p>Hypoglycemia</p> <p>In both of their Phase 3 Clinical Trial programs, NovoLog[®] and Humalog were compared with regular human insulins (please see above for explanation). In this section we will provide the hypoglycemia results from those clinical trials. In NovoLog[®] trials, severe hypoglycemia was defined as hypoglycemia for which patients could not self-treat (i.e., required the assistance of another person or hospitalization) [2].</p> <p>Table 2 shows rates of severe hypoglycemia observed in pivotal trials of rapid-acting insulins. The severe hypoglycemia rates for NovoLog[®] and Humalog were similar to regular human insulin [2], [5].</p> <p>3. Clinical Outcomes of FIASP[®]</p> <p>Key Takeaways</p> <ul style="list-style-type: none"> • FIASP[®] and Lyumjev Phase 3 clinical trials presented in this section were treat-to-target, which means the overall HbA1c reductions are expected to be the same across treatment groups. • In general, FIASP[®] shows non-inferiority to NovoLog[®] and Lyumjev shows non-inferiority to Humalog in their ability to lower HbA1c and in hypoglycemia rates in T1D and T2D, although some evidence points to greater efficacy and lower hypoglycemia rates with FIASP[®]. • FIASP[®] outperforms NovoLog[®] and Lyumjev outperforms Humalog in terms of reducing 1-hour PPG increments in patients with T1D and T2D. <p>The Phase 3 Clinical Trial program for FIASP[®] used NovoLog[®] as its active comparator while the program for Lyumjev used Humalog as its active comparator. FIASP[®] was developed to achieve a faster onset of action than currently available rapid acting insulin analogs. NovoLog[®] was applied as the active comparator for FIASP[®] to confirm its clinical efficacy and safety, which at the time was one of the most broadly used prandial insulins on the US market and thus reflective of the current standard of care. FIASP[®] pivotal trials were conducted to test non-inferiority with NovoLog[®] while Lyumjev’s pivotal trials included comparisons with Humalog when administered via subcutaneous daily injection and continuous subcutaneous infusion in adults with T1D and T2D [9] [10]. These trials are summarized below by HbA1c, PPG, and hypoglycemia.</p> <p>Note: There is no pivotal head-to-head trial comparing efficacy of FIASP[®] with Lyumjev, so no direct comparative effectiveness statements can be made from these studies.</p> <p>a. Effectiveness of FIASP[®] and Lyumjev</p> <p>HbA1c</p> <p>Once again it is important to note that all studies were treat-to-target where insulin doses are titrated to enable</p>



Question	Sub-Question	Response
		<p>patients to achieve a known and validated target level of glycemic control. For this reason, overall HbA1c reductions in treat-to-target studies are expected to be the same among treatment groups, with no differences in efficacy expected [7].</p> <p>Once again, as per FDA directive, clinical development program for FIASP® used non-inferiority for change in HbA1c as the primary endpoint [6]. It is important to note that due to FDA guidance the programs were designed as treat-to-target trials where insulin doses in both comparator and investigational arms are titrated to achieve a known and validated target level for glycemic control [6]. For this reason, overall HbA1c reductions in treat-to-target studies are expected to be the same among treatment groups, with no differences in efficacy expected [7].</p> <p>Four pivotal, treat-to-target, non-inferiority clinical trials were performed on FIASP® (subcutaneous injection) in adults: two trials in patients with T1D and two in patients with T2D [11] [12] [13] [14]. FIASP® demonstrated non-inferiority in HbA1c reduction compared to NovoLog® in patients with T1D (ONSET 8 [11]) and T2D (ONSET 2 [13] and 9 [14]). One trial in patients with T1D (ONSET 1) showed that mealtime FIASP® significantly reduced HbA1c versus NovoLog® (p = 0.0003) [12]. Lyumjev demonstrated non-inferiority with Humalog in adults with both T1D and T2D [15] [16].</p> <p>Table 3 summarizes HbA1c results from each product’s respective pivotal trials when administered via subcutaneous daily injections [9] [10].</p> <p>Pivotal trials for FIASP® and Lyumjev were also conducted for continuous subcutaneous infusion administration in patients with T1D [9], [10], [17]. Both FIASP® and Lyumjev were found to be non-inferior to NovoLog® and Humalog, respectively. Results for mean change from baseline HbA1c for FIASP® and Lyumjev are summarized in Table 4 below.</p> <p>Post-prandial Glucose</p> <p>Furthermore, all FIASP® trials revealed that mealtime administration of FIASP® outperformed NovoLog® in terms of reducing 1-hour PPG increments (p<0.05 in all studies) [11] [12] [13] [14]. Similarly, significantly lower 1-hour PPG excursions were reported with Lyumjev compared to Humalog [15] [16].</p> <p>b. Safety of FIASP® and Lyumjev</p> <p>Hypoglycemia</p> <p>As with all insulin products, the most common adverse event with FIASP® is hypoglycemia. In NovoLog® pivotal trials, severe hypoglycemia was defined as an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. 9]. Safety profiles and overall rates of severe or blood glucose-confirmed hypoglycemia were mostly similar between FIASP® and NovoLog® in most pivotal studies [11] [12] [13] [17]. A multicenter trial in adults with T2D found a lower relative risk of severe hypoglycemia for FIASP® compared to NovoLog® (RR: 0.81; p = 0.019) [14].</p> <p>Table 4 summarizes the safety profile of FIASP® and Lyumjev studied in their respective pivotal trials [9] [10].</p>



Question	Sub-Question	Response
		<p>4. Beyond Clinical Outcomes – Improving Patient Experience</p> <p>Key Takeaways</p> <ul style="list-style-type: none"> • The introduction of novel delivery systems, including pens and pumps, represented a key advancement in diabetes care for patients. • In addition to improved treatment satisfaction, quality of life, and adherence, insulin pens offer safety related to dosing accuracy compared to vials/syringes. • A 16-week, open-label, single arm study showed that patients using insulin pumps preferred using NovoLog® over Humalog. <p>Diabetes is a multi-faceted chronic condition for which treatment success goes beyond clinical outcomes and depends on patient satisfaction, acceptance, adherence, and quality of life. Diabetes has a high treatment burden wherein patients are required to undertake strict self-management and adhere to their treatment protocols at the cost of their quality of life. From this standpoint, the introduction of the pen delivery system represented a key advancement in diabetes care for patients [18].</p> <p>Both NovoLog® and FIASP® are available in pen devices in addition to vials. Insulin pens have several advantages over the vial/syringe method of insulin delivery, including improved patient satisfaction and adherence, greater ease of use, superior accuracy for delivering small doses of insulin, greater social acceptability, and less reported injection-site pain [19]. Beyond the impact on patient satisfaction and quality of life, patient safety related to dosing accuracy is better with the use of insulin pens versus the vial/syringe method [20]. Patients using vial/syringe are at greater risk of drawing up an incorrect insulin dose, with an estimated relative error of 19%, which is a significant risk and concern [21]. An open-label, randomized, crossover study showed that 73% of patients felt more confident in the accuracy of the insulin dose delivered with the pen while a separate study evaluating patient satisfaction associated with the method of insulin administration found that those using pens were more likely to adhere to their insulin therapy, resulting in fewer hypoglycemic episodes and reduced healthcare costs [21], [22].</p> <p>For people living with diabetes who find injections difficult, an insulin pump can bring welcome relief. Insulin pumps are small, computerized devices that deliver prandial insulin as a surge ("bolus") dose, at the patient's direction, around mealtime. This delivery mimics the body's normal release of insulin and can integrate with the patient's continuous glucose monitor, thereby improving convenience, satisfaction, and treatment adherence. A 16-week, open-label, single arm study was conducted to compare the use of NovoLog® via continuous subcutaneous infusion in 513 adults with either T1D or T2D who previously used Humalog [23]. This study reported average overall Insulin Treatment Satisfaction Questionnaire (ITSQ) scores for NovoLog® were significantly greater than for Humalog (82.9 vs. 81.2; p <0.001) [23]. This was driven by subjects feeling less bothered by symptoms of low blood sugar, less worried about experiencing low blood sugar episodes during the night, more satisfied with the stability of their blood sugar levels, and more pleased with their level of blood sugar control. In addition, subjects believed that NovoLog® therapy was less time consuming and less burdensome to manage than their previous experience with</p>



Question	Sub-Question	Response
		<p>Humalog. Furthermore, subjects using NovoLog® had less of a tendency to feel down or depressed and had more favorable perceptions of pain and physical discomfort [23].</p> <p>5. Healthcare Resource Use</p> <p>Several studies quantify the direct and indirect costs of diabetes in the U.S. and how successful control of the disease can offset these costs. An ADA-commissioned study (2018) estimated the national cost of diabetes at \$327 billion, 73% of which was driven by direct healthcare expenditures attributed to diabetes and 27% driven by lost productivity from work-related absenteeism, reduced productivity, unemployment, and premature mortality [24]. People with diabetes incurred 24.8% of U.S. hospital inpatient days, 13.9% of which were specifically attributed to a diagnosis of diabetes. People with diabetes represent an even higher percentage of nursing/residential facility days (26.1% of the total incurred by the U.S. population in 2016) and incurred high percentages for physician office visits (21.5%), emergency department visits (12.2%), hospital outpatient visits (19.2%), and home health visits (21.2%). Also, approximately 61% of healthcare expenditures attributed to diabetes are used by populations older than 65 years, much of which is associated with vascular complications including cardiovascular-related care.</p> <p>There is robust evidence linking high PPG levels with the development of vascular complications [25]. The Diabetes Control and Complications Trial (DCCT) showed definitively that better glycemic control in patients with T1D is associated with 50-76% reduction in rates of development and progression of microvascular complications such as retinopathy, neuropathy, and diabetic kidney disease [26]. Insulin therapies that control prandial glucose, like NovoLog® and FIASP®, can offset health-related resource utilization that would otherwise be incurred by vascular complications linked with high PPG levels [27].</p>
	<p>Hyperlink to Citation - Additional Materials for Question 28</p>	<p>[REDACTED]</p>
	<p>Hyperlink to Table/Charts/Graphs - Additional Materials for Question 28</p>	<p>[REDACTED]</p>
	<p>Evidence Submitted include a cost-effectiveness measure?</p>	<p>N</p>



Question	Sub-Question	Response
	What type of Evidence is shown?	
Question 29: Comparative Effectiveness on Specific Populations	Response to Question 29	<div style="background-color: black; width: 100%; height: 40px; margin-bottom: 10px;"></div> <p>For clarity purposes, Novo Nordisk provides its responses to Section I, “Evidence About Selected Drugs and Their Therapeutic Alternatives Form,” including this response, as a complete PDF document. This was uploaded within “Additional Materials for Questions 28”.</p> <p>Novo Nordisk Inc. is providing this summary of information in response to an unsolicited inquiry by CMS. Please see cited references for full discussion of study design and results.</p> <p>In our responses to Q27 and Q28 we have outlined evidence for NovoLog® and FIASP® as well as their therapeutic alternatives in adults with type 1 diabetes (T1D) and type 2 diabetes (T2D).</p> <p>In the sections below, we discuss evidence relevant for specific subpopulations – pediatric patients, older adults, and patients with renal impairment. We will then touch on innovations in delivery methods for insulin - pens and pumps - and their benefits in specific subpopulations.</p> <p>1. Pediatric Patients</p> <p>Key Takeaways</p> <ul style="list-style-type: none"> • NovoLog® and Humalog are non-inferior to regular human insulin in HbA1c reduction and hypoglycemia rates in pediatric patients with T1D. However, continuous subcutaneous infusion of NovoLog® outperforms Humalog in achieving age-specific American Diabetes Association (ADA) recommended HbA1c goals in these patients. • Not only is FIASP® non-inferior to NovoLog® in terms of HbA1c outcomes and hypoglycemia rates, but it also offers improved flexibility, as it can be administered post-meal with similar efficacy results as mealtime FIASP®. Elevated post-prandial glucose levels may be associated with long term complications. <p>As a reminder, the Phase 3 Clinical Trial programs for NovoLog® and Humalog used regular human insulin as their active comparator [1], [2]. For the NovoLog® clinical trial program, regular human insulin was chosen as the active comparator because it was the only prandial insulin available when the Phase 3 program was designed. Humalog was the first rapid-acting human insulin analog available on the market and did not receive FDA approval nor become commercially available until 1996, which was after the development and initial implementation of the NovoLog® Phase 3a clinical trial program.</p> <p>a. Clinical Effectiveness and Safety of NovoLog®</p> <p>Both NovoLog® and Humalog are indicated to improve glycemic control in children with T1D and T2D. Pivotal trials of NovoLog® and Humalog indicate that they are non-inferior to regular human insulin in reducing</p>



Question	Sub-Question	Response
		<p>HbA1c from baseline [1], [2]. In a 24-week, parallel-group study of pediatric patients with T1D aged 6-18 years, subcutaneous injection of NovoLog® achieved glycemic control comparable to regular human insulin, as measured by change in HbA1c [1]. Similar results were seen in another trial in children with T1D (n=26) aged 2 to 6 years [1]. However, a 2008 randomized clinical trial of 298 pediatric patients with T1D using continuous subcutaneous infusions found that NovoLog® outperformed Humalog in achievement of age-specific ADA recommended HbA1c goals (NovoLog®, 59.7% vs Humalog, 43.8%, P=0.040) [3]. These trials also report comparable hypoglycemia rates between NovoLog® and regular human insulin, and Humalog and regular human insulin.</p> <p>b. Clinical Effectiveness and Safety of FIASP®</p> <p>Unpredictable eating habits of children with T1D is a significant problem that parents need to account for when considering insulin treatment. It can be difficult to determine the amount of food a child will eat, thereby complicating insulin dosing decisions before mealtime [4]. The ability to inject FIASP® post-prandially (after a meal) provides flexibility to address this concern helping to keep children within the target glycemic level with less risk for excursions. Over the life of the child, this can be an important contributor of long-term benefit and help delay disease progression.</p> <p>A randomized controlled trial of children aged 2 to 17 years with T1D found that at week 26, mealtime and post meal FIASP® were non-inferior to NovoLog® in terms of HbA1c change from baseline [5]. Change from baseline in 1-hour postprandial glucose significantly favored mealtime FIASP® versus NovoLog® at breakfast, main evening meal, and over all meals (P < 0.01 for all) [5]. No statistically significant differences in hypoglycemia rates were observed. Additionally, there was no significant difference in mean self-measured blood glucose for post-meal FIASP® versus mealtime FIASP® [5]. The overall rate of severe hypoglycemic episodes was comparable between post-meal and mealtime FIASP® (1.11 [95% CI 0.90 - 1.37]) [5]. These results indicate that there is improved flexibility with FIASP® administration, as it can be administered post-meal with similar efficacy results.</p> <p>In summary, FIASP® has the flexibility to be dosed at the start of a meal or within 20 minutes after starting the meal, giving parents a more reliable and user-friendly treatment to help manage their child’s diabetes [6].</p> <p>2. Older Adults (65+)</p> <p>Key Takeaways</p> <ul style="list-style-type: none"> • Older adults (aged 65+) - a demographic with a higher rate of T2D and higher rates of serious co-morbidities - were well-represented in Novo Nordisk Inc.’s clinical trials and safety and effectiveness of NovoLog® and FIASP® were consistent in these patients. <p>a. Epidemiology and Importance of Insulins in Older Adults</p> <p>More than 1 in 4 adults over the age of 65 years have diabetes. While most older adults have T2D, this dynamic is rapidly changing due to improved survival of adults living with T1D [7]. Older adults with diabetes have higher rates of premature death, functional disability, muscle loss, and comorbidities (including hypertension, coronary heart</p>



Question	Sub-Question	Response
		<p>disease, and stroke) compared to those without diabetes [8]. Diabetes care for older adults is complicated by the presence of common geriatric syndromes that can impede individuals' ability to self-manage their disease (e.g., frailty, cognitive impairment, depression). At the same time, hypoglycemic events have been linked to increased risk of dementia and cognitive decline [9]. Older adults diagnosed with diabetes are also at increased risk for other geriatric-related conditions, such as falls and osteoporosis [9].</p> <p>b. Effectiveness and safety in older adults</p> <p>NovoLog[®]'s pivotal trials included an assessment of efficacy in geriatric populations. Of the total number of patients (n=1,375) treated with NovoLog[®] in three controlled clinical studies, 2.6% (n=36) were 65 years of age or older. Half of these patients had T1D and the other half had T2D. The HbA1c response to NovoLog[®] did not differ by age in these trials [1]. The pharmacokinetic and pharmacodynamic properties of NovoLog[®] and regular human insulin were investigated in a single dose study in 18 subjects with T2D who were ≥ 65 years of age. The relative differences in pharmacokinetics and pharmacodynamics in geriatric patients with T2D between NovoLog[®] and regular human insulin were similar to those in younger adults indicating that it has a similar effect in this population as it does in adults [1].</p> <p>Similarly, in three controlled clinical studies, 192 of 1,219 (16%) FIASP[®]-treated patients with T1D or T2D were 65 years or older and 24 (2%) were 75 years or older [6]. The trials found consistent safety and effectiveness results between these elderly patients and younger adults [6].</p> <p>3. Renal Impairment</p> <p>Key Takeaways</p> <ul style="list-style-type: none"> • Lowering blood glucose delays the onset and progression of kidney damage • Renal impairment does not affect the pharmacokinetics of NovoLog[®] or FIASP[®], thereby enabling their use in this population. <p>The ADA estimates that approximately 20–40% of people with diabetes will develop diabetic chronic kidney disease (CKD) [10]. The presence of CKD significantly increases cardiovascular risks: almost half of patients with CKD stage 4 and 5 develop cardiovascular disease [11]. CKD can progress to end-stage renal disease (ESRD), which requires dialysis or kidney transplantation, reduces quality of life, and can lead to premature mortality [12]. Large, randomized studies have shown that lowering blood glucose delays the onset and progression of kidney damage as measured by urinary albumin excretion and estimated glomerular filtration rate [10], [13]. In patients with CKD, a reduction in clearance rates may present dosing challenges for any medications ingested and cleared in the kidneys, as the resultant prolonged duration of these medications in the bloodstream could have unanticipated adverse effects. Since NovoLog[®] and FIASP[®] are recognized for their rapid onset and shorter duration, this may mitigate these concerns [14]. Furthermore, a study assessing the effects of a single dose of NovoLog[®] in patients with comorbidities, including patients with diabetes and renal impairment, found that renal impairment does not affect the pharmacokinetics of NovoLog[®] in a clinically significant manner [15]. Thus, NovoLog[®] and FIASP[®] are effective treatment strategies in this population of CKD patients with T1D and T2D.</p>



Question	Sub-Question	Response
		<p>4 - Common Methods of Administration and Their Benefits in Specific Subpopulations</p> <p>Key Takeaways</p> <ul style="list-style-type: none"> • Patient safety related to dosing accuracy is better with the use of insulin pens versus the vial/syringe method. • 85% of patients reported they found it easier to read the insulin dose scale with a pen compared with a vial and syringe. • A significantly greater percentage of patients were adherent after switching to an insulin pen (54.6% versus 36.1%, $p < 0.01$) and the likelihood of hypoglycemic events was reduced by 50%. <p>a. Administration by vial and syringe Traditionally, insulin is provided in a vial and administered via a syringe, which presents a series of challenges. For some, the vial/syringe can be disruptive and draining, and it can also be associated with anxiety from pain or fear associated with the needles, and the fear of social stigma around the use of syringes [16]. Also, multiple comorbidities such as dementia, vision loss, neuropathies, poor mobility, and poor manual dexterity can affect the patient’s ability to self-inject insulin especially in the elderly population [17].</p> <p>b. Novo Nordisk Inc. introduces first insulin pen Given the challenges of administering insulin by vial and syringe, Novo Nordisk Inc. invested in the development of innovative delivery methods for its insulins and continues to do so. Novo Nordisk Inc. launched the very first insulin pen (NovoPen®) in 1985 [18] and has continued to improve their functionality to better meet patient needs (e.g., NovoLog® FlexPen®, FIASP® FlexTouch®, NovoPen Echo®) [19], [20], [21]. Patient safety related to dosing accuracy is better with the use of insulin pens versus the vial/syringe method [22]. Patients using vial/syringe are at greater risk of drawing up an incorrect insulin dose, with an estimated relative error of 19% in dosing accuracy, which is a significant risk and concern for the elderly [17]. By contrast, pens have a dial that is turned to select the correct dose (no reading of a syringe required) and the device clicks as the patient selects each unit [20], which helps individuals with impaired vision or dexterity problems select the correct dose [23], [17]. In an open-label randomized crossover study, 85% of patients reported that they found it easier to read the insulin dose scale with the pen compared with the vial/syringe [24]. Seventy-three percent (73%) of patients in the study felt more confident in the accuracy of the insulin dose delivered with the pen, compared with 19% for the vial/syringe [24]. A large review specific to studies in the elderly population found that the ability to dial up a dose in a pen led to higher accuracy and reliability than syringe dosing, particularly for lower doses often used by the elderly [17]. Additionally, the compact, portable, and easy to grip structure of pens benefits those with manual dexterity impairments, while the less painful injections and overall ease of use likely contribute to patient preference for insulin pens [17]. A study evaluating patient satisfaction associated with the method of insulin administration found that those using pens reported more comfort and confidence with their device and were thus more likely to adhere to their insulin therapy, resulting in fewer hypoglycemic episodes and reduced healthcare costs [25]. Additionally, a retrospective</p>



Question	Sub-Question	Response
		<p>claims analysis of 1156 patients with T2D examined the association of insulin delivery method and adherence by examining outcomes before and after switching to an insulin analog pen [26]. A significantly greater percentage of patients were adherent after switching to the pen device (54.6% versus 36.1%, $p < 0.01$) and the likelihood of hypoglycemic events was reduced by 50% after switching to an insulin pen (Odds ratio = 0.50; 95% Confidence interval, 0.37–0.68; $p < 0.05$) [26]. This is an important consideration in the elderly population where adherence is negatively impacted by multimorbidity, cognitive impairment, and complex medication regimens [27]. Additionally, adjusted mean annual diabetes-related and all-cause healthcare costs per patient significantly decreased after switching to the insulin pen (\$16,359 to \$14,769; $p < 0.01$, and \$1,415 to \$627; $p < 0.01$, respectively) [26]. Thus, Novo Nordisk Inc.’s innovation in insulin delivery methods has filled a significant unmet need in patients with T1D and T2D, especially in specific subpopulations like older adults who can benefit from ease of administration of their medications.</p> <p>c. Insulin pumps</p> <p>Advancements in the development of modern insulin including rapid-acting analogs have spurred progress in insulin delivery devices and glucose monitoring technology [28]. One of these advancements is insulin pumps with rapid-acting insulin formulations which are mainly used by individuals living with T1D, although 10% of pump users live with T2D [29]. The use of insulin pumps has increased dramatically in the United States from <7,000 users in 1990 to nearly 100,000 in 2000 and >350,000 in 2022 [30]. There are many advantages to using an insulin pump compared to individual subcutaneous injections from which pediatric and elderly patients benefit, including precision, flexibility, and convenience.</p> <ol style="list-style-type: none"> 1. Insulin pump therapy allows for more precise dosing which ultimately leads to improved outcomes. Many studies and systematic reviews have demonstrated improved glycemic control and a reduction in hypoglycemia with insulin pump therapy compared to injections in pediatric and adult populations living with T1D [31], [32], [33], [34], [35], [36], [37], [38]. 2. Insulin pumps continuously deliver insulin instead of requiring a patient to inject separate injections for their basal insulin and mealtime insulin. Additionally, anytime changes in insulin dosing are needed, either the basal and/or mealtime component doses can easily be programmed into the pump which then begins administering new doses immediately, while those using injections must manually adjust to each new regimen. Thus, pump therapy allows for increased flexibility, especially when outside the home, which is especially important for pediatric patients. 3. Where injections require administration (injection under the skin) before each meal or snack, a push of a button can deliver prandial insulin via pumps, thereby offering patients an alternative with fewer daily injections. This is a very important advantage not only in adults, but also pediatric and elderly patients. <p>In summary, Novo Nordisk Inc.’s investment in novel delivery systems has enabled improved patient experience in specific subpopulations such as pediatric and elderly patients. Newer methods of insulin administration offer several</p>



Question	Sub-Question	Response
		<p>advantages to these specific subpopulations which can improve clinical outcomes in these patients. In summary, Novo Nordisk Inc.'s investment in novel delivery systems has enabled improved patient experience in specific subpopulations such as pediatric and elderly patients. Newer methods of insulin administration offer several advantages to these specific subpopulations which can improve clinical outcomes in these patients.</p>
	<p>Hyperlink to Citation - Additional Materials for Question 29</p>	<p>[REDACTED]</p>
	<p>Hyperlink to Table/Charts/Graphs - Additional Materials for Question 29</p>	<p>[REDACTED]</p>
	<p>Evidence Submitted include a cost-effectiveness measure?</p>	<p>N</p>
	<p>What type of Evidence is shown?</p>	<p>[REDACTED]</p>
<p>Question 30: Addressing Unmet Medical Needs</p>	<p>Response to Question 30</p>	<p>[REDACTED]</p> <p>For clarity purposes, Novo Nordisk provides its responses to Section I, "Evidence About Selected Drugs and Their Therapeutic Alternatives Form," including this response, as a complete PDF document uploaded within "Additional Materials for Questions 28".</p> <p>Novo Nordisk Inc. is providing this summary of information in response to an unsolicited inquiry by CMS. Please see cited references for full discussion of study design and results.</p> <p>Rapid-acting insulin analogs including NovoLog® and FIASP® address four critical unmet needs:</p> <ol style="list-style-type: none"> 1. Improvement in Post-Prandial Glucose Control <p>Given intra-patient variability and day-to-day changes in activity and food consumption, basal (long-acting) insulins</p>



Question	Sub-Question	Response
		<p>are often insufficient in achieving HbA1c levels [1], [2]. Although exact estimates vary, only 21.0% of patients with type 1 diabetes (T1D) and 38.9% of patients with type 2 diabetes (T2D) utilizing basal insulins achieve HbA1c goals [3], [4]. A large, real-world retrospective analysis of almost 40,000 patients with T2D on basal insulin in the US found that 73% of patients did not meet HbA1c goals, and that rapid-acting insulin was added for 32.6% of patients overall, including 43% of ongoing users of basal insulin [5]. This pattern was also seen for patients who did not achieve fasting blood glucose goals on basal insulin alone; 27.3% of those patients added a rapid-acting insulin [5]. HbA1c levels are determined by both fasting plasma glucose (FPG) and post-prandial plasma glucose (PPG) levels, and therefore effective management of both components is essential [6]. Many patients have acceptable FPG levels yet fail to achieve the recommended HbA1c target <7%. Studies have demonstrated that PPG contributes significantly to overall HbA1c levels, with a greater relative effect (up to 70%) observed when patients are nearing HbA1c levels of 7% [7]. However, post-prandial hyperglycemia or elevated PPG level after meals is still common in patients with diabetes [8]. Rapid-acting insulin analogs like NovoLog® and ultra-rapid acting insulin analogs like FIASP® closely match the physiological insulin profile of a person without diabetes when compared with regular human insulin to ensure better glycemic control [9].</p> <p>Prandial insulins address a key unmet need in diabetes care by providing better glucose control to avoid adverse effects of high blood glucose following meals. Additionally, without prandial insulins, patients face the risk of over-basalization, or being prescribed excessive basal insulin doses to achieve glycemic targets, which ultimately results in a proportionally higher risk of hypoglycemia and weight gain [10], [11]. Therefore, rapid-acting and ultra-rapid acting insulins address a key unmet need of treatment intensification, particularly around meals, for patients living with T1D and T2D.</p> <p>2. Avoidance of Long-term Complications Complications due to poor glycemic control is a key contributor to the burden of diabetes. In the Diabetes Control and Complications Trial (DCCT), compared to patients on intensive therapy (aimed at achieving levels of glycemia as close to the nondiabetic range as safely possible), patients on conventional therapy (relatively poor glycemic control), had a higher incidence of retinopathy, nephropathy, and cardiovascular complications [12]. Furthermore, the presence of complications is associated with a significant increase in the likelihood of having depression or anxiety [13]. Complications due to poor glycemic control is a significant contributor to the cost of care in diabetes and is estimated to account for 53% of all diabetes-related costs [14]. There is always a need for newer and improved products that effectively keep blood sugar levels under control and prevent long term complications in T1D and T2D.</p> <p>3. Overcoming Restrictions on Daily Activities and Challenging Mealtime Dosing Requirements Although American Diabetes Association (ADA) guidelines recommend that rapid-acting insulin analogs be injected before meals as indicated [15], evidence suggests that many patients do not follow recommendations and dose insulin after their meal [16], [17], [18]. This can result in poor post-prandial glucose control which can lead to short</p>



Question	Sub-Question	Response
		<p>and long-term complications. An analysis of data from the T1D Exchange registry involving 21,533 patients revealed that 32% of patients dosed insulin after their meal [16]. An independent, online survey of adults with T1D, and parents and physicians of children with T1D found that 91% of adults and 97% of parents experienced at least one major challenge with mealtime insulin dosing [19]. Reported challenges that occurred at least once a week included eating more or less food than anticipated after dosing mealtime insulin (70% of adults and 81% of parents of children); needing to eat additional food as a corrective action to prevent hypoglycemia as a result of eating a meal that had less carbohydrates than anticipated (58% of adults and 70% of parents of children); and needing to administer additional corrective insulin after consuming more food than was anticipated (57% of adults and 65% of parents of children) [19]. FIASP®’s improved time-action profile, more rapid onset of action, and demonstrated efficacy can help alleviate the need for corrective actions after meals by allowing for more flexible insulin dosing around meals while mitigating concerns about PPG excursions [19].</p> <p>4. Novel Delivery Systems That Respond to Evolving Patient Needs Advancements in modern insulin development including rapid-acting and ultra-rapid analogs have spurred progress in insulin delivery devices and glucose monitoring technology [20]. One of these advancements is insulin pumps which generally use rapid-acting insulin formulations and are mainly used by individuals living with T1D, although 10% of pump users live with T2D [21]. The use of insulin pumps has increased dramatically in the United States from <7,000 users in 1990 to nearly 100,000 in 2000 and >350,000 in 2022 [22]. Advantages of insulin pumps include precise dosing, flexibility (continuous insulin delivery and programmability to adjust dose), and convenience (push-of-a-button insulin delivery) compared to vials and syringes. Insulin pens represent another technological advance which are more convenient, less painful, easily storable and transportable, have greater ease of use, and greater social acceptability compared to vials/syringes [23], [24].</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>For 100 years, Novo Nordisk Inc. has been committed to driving change to improve treatment for individuals living with type 1 diabetes (T1D) and type 2 diabetes (T2D), from more effective medicines to better delivery systems that make management simpler, more convenient, and reduce the burden of living with a chronic disease. As part of its expansive diabetes R&D program, Novo Nordisk Inc. has made significant investments in developing rapid-acting NovoLog® (approved 7/7/2000) and ultra-rapid acting FIASP® (approved 9/28/2017).</p> <p>Both NovoLog® and FIASP® are indicated to improve glycemic control in adult and pediatric patients with T1D and T2D. While their indications are the same, NovoLog® and FIASP® are two unique products which belong to different classes of prandial insulins, NovoLog® in the rapid-acting class and FIASP® in the ultra-rapid acting class. The American Diabetes Association (ADA) Guidelines states that the preferred insulin regimen for patients with T1D is a long-acting insulin with flexible doses of an ultra-rapid acting analog or a rapid-acting analog at meals. In a randomized, single-centered, double-blind, 3-period crossover study in 51 patients with T1D, it was shown that FIASP® appears in the bloodstream two times faster than NovoLog®. FIASP® also has more flexible subcutaneous administration as it can be dosed at the start of a meal or 20 minutes after starting a meal, while NovoLog® is to be dosed before or within 5-10 minutes of the start of the meal. Finally, three pivotal, treat-to-target, non-inferiority clinical trials showed that mealtime administration of FIASP® outperformed NovoLog® in terms of reducing the post-prandial glucose (PPG) control, or glucose control after a meal, at 1-hour after patients were provided the same amount of carbohydrate.</p> <p>For the reasons mentioned above as well as the additional details discussed within Section I, the most “clinically comparable therapeutic alternative” to NovoLog® are other rapid-acting insulins Humalog and its follow-on biologic ADMELOG, while the most “clinically comparable therapeutic alternative” to FIASP® is another ultra-rapid insulin,</p>



Question	Sub-Question	Response
		<p>Lyumjev. It is important to note that ADMELOG’s indication differs from both NovoLog®’s and Humalog’s as it is indicated to improve glycemic control in adults and pediatric patients 3 years and older with T1D and only adults with T2D. [REDACTED]</p> <p>When comparing these products, it is important to consider several different factors including clinical efficacy, safety, patient experience, and how they are administered, which also plays a major role in patient experience. Starting with clinical efficacy, the outcomes that should be considered are Hemoglobin A1c (HbA1c), PPG control, and safety. As explained in the response to question 28, there is no simple and straightforward way to compare the clinical efficacy between therapeutic alternatives. First, in their pivotal trials, both NovoLog® and Humalog were compared to regular human insulin as that was the only prandial insulin available at that time. Over 15 years later, FIASP® and Lyumjev, both ultra-rapid acting insulins, were compared to rapid-acting insulins during their pivotal clinical trial programs, as these represented the standard of care. Therefore, while data from these clinical trials has been presented and summarized, no direct head-to-head clinical comparisons can be made between NovoLog® and Humalog or FIASP® and Lyumjev. In addition to this, both clinical trial programs were designed as treat-to-target per FDA guidance, meaning that the patients enrolled had their insulin titrated to achieve a known and validated HbA1c score. While it is important to consider the impact rapid-acting and ultra-rapid acting insulins have on outcomes compared to their comparators, it is difficult given the structure of the clinical trials.</p> <p>An important result from the trials was NovoLog® and FIASP®’s impact on PPG control versus their comparators. In patients with T1D, when compared with regular human insulin, NovoLog® provided significantly superior PPG control. The same can be said for FIASP® versus its comparator NovoLog®. PPG levels contribute significantly to overall HbA1c. The Diabetes Control and Complications study (DCCT) showed definitively that better glycemic control in patients with T1D is associated with a reduction in rates of development and progression of microvascular complications such as retinopathy, neuropathy, and diabetic kidney disease, while there is robust evidence linking high PPG levels with the development of vascular complications. Approximately 61% of healthcare expenditures in diabetes are attributed to elderly patients over 65 years of age, much of which is represented by vascular complications including cardiovascular-related care. Owing to their impact on PPG levels, NovoLog® and FIASP® are important treatment options that can potentially have a positive impact on complications and healthcare resource use in patients with T1D and T2D.</p> <p>Rapid-acting and ultra-rapid acting insulins like NovoLog® and FIASP®, respectively, improve patient experience. An independent, online survey of adults with T1D, and parents and physicians of children with T1D found that 91% of adults and 97% of parents experienced at least one major challenge with mealtime insulin dosing. Therefore, products such as FIASP®, which can be administered at the beginning of a meal or 20 minutes after, are particularly valuable as it allows patients more flexibility when compared to products which must be dosed before a meal. NovoLog® and FIASP® are both available in multiple modes of administration which must be considered when</p>

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Question	Sub-Question	Response
		<p>determining the value of each NDC. Patients using vial/syringe are at greater risk of drawing up an incorrect insulin dose, with an estimated relative error of 19%, which is a significant risk and concern for patients, especially elderly patients. An open-label randomized crossover study showed that 73% of patients felt more confident in the accuracy of the insulin dose delivered with a pen while a separate study evaluating patient satisfaction associated with the method of insulin administration found that those using pens were more likely to adhere to their insulin therapy, resulting in fewer hypoglycemic episodes and associated healthcare costs.</p>

Tables for Q28

Table 1. NovoLog® and Humalog HbA1c Pivotal Trial Results: Subcutaneous Daily Injections

Characteristic	NovoLog®
Type 1 Diabetes	
Population	Adults
Rapid Acting Insulin Cohort Arm (N)	596
Mean Baseline HbA1c	7.9
Mean Change from Baseline HbA1c	-0.1
Type 2 Diabetes	
Population	Adults
Population Size	90
Mean Baseline HbA1c	8.1
Mean Change from Baseline HbA1c	-0.3
Characteristic	Humalog
Type 1 Diabetes	
Population	Adults & Adolescents
Rapid Acting Insulin Cohort Arm (N)	81
Mean Baseline HbA1c	8.2
Mean Change from Baseline HbA1c	-0.1
Type 2 Diabetes	
Population	Adults
Population Size	722
Mean Baseline HbA1c	8.2
Mean Change from Baseline HbA1c	-0.7

Note: These data are from separate clinical trials comparing NovoLog® to regular human insulins and Humalog to regular human insulins. These trials did NOT compare NovoLog® and Humalog head-to-head and no conclusions about comparative effectiveness of NovoLog® and Humalog should be drawn.

Table 2. Hypoglycemia Rates in Pivotal Trials of NovoLog® and Humalog: Subcutaneous Daily Injections

Characteristic	NovoLog®
Type 1 Diabetes	
Population	Adults
Population Size	596
Patients with Severe Hypoglycemia	17%
Type 2 Diabetes	
Population	Adults
Population Size	90
Patients with Severe Hypoglycemia	10%
Characteristic	Humalog
Type 1 Diabetes	
Population	Adults & Adolescents
Population Size	81
Patients with Severe Hypoglycemia	17%
Type 2 Diabetes	
Population	Adults

Population Size	722
Patients with Severe Hypoglycemia	2%

Note: These data are from separate clinical trials comparing NovoLog® to regular human insulins and Humalog to regular human insulins. These trials did NOT compare NovoLog® and Humalog head-to-head and no conclusions about safety of NovoLog® and Humalog should be drawn.

Table 3. FIASP® and Lyumjev HbA1c Pivotal Trial Results: Subcutaneous Daily Injections

Characteristic	Mealttime FIASP®
Type 1 Diabetes	
Population	Adults (ONSET 1)
Population Size	381
Mean Baseline HbA1c	7.6
Mean Change from Baseline HbA1c	-0.32
Type 2 Diabetes	
Population	Adults (ONSET 2)
Population Size	345
Mean Baseline HbA1c	8.0
Mean Change from Baseline HbA1c	-1.38
Characteristic	Mealttime Lyumjev
Type 1 Diabetes	
Population	Adults
Population Size	451
Mean Baseline HbA1c	7.3
Mean Change from Baseline HbA1c	-0.12
Type 2 Diabetes	
Population	Adults
Population Size	336
Mean Baseline HbA1c	7.3
Mean Change from Baseline HbA1c	-0.36

Note: These data are from separate clinical trials comparing FIASP® to NovoLog® and Lyumjev to Humalog. These trials did NOT compare FIASP® and Lyumjev head-to-head and no conclusions about comparative effectiveness of these products should be drawn.

Table 4. Hypoglycemia Rates in Pivotal Trials of FIASP® and Lyumjev

Characteristic	Mealttime FIASP®
Type 1 Diabetes (Single Injection)	
Population	Adults
Population Size	386
Patients with Severe Hypoglycemia	6.7%
Type 1 Diabetes (Continuous Subcutaneous Infusion)	
Population	Adults
Population Size	236
Patients with Severe Hypoglycemia	4.7%
Type 2 Diabetes (Single Injection)	
Population	Adults
Population Size	341
Patients with Severe Hypoglycemia	3.2%

Characteristic	Mealtime Lyumjev
Type 1 Diabetes (Single Injection)	
Population	Adults
Population Size	451
Patients with Severe Hypoglycemia	5.5%
Type 1 Diabetes (Continuous Subcutaneous Infusion)	
Population	Adults
Population Size	215
Patients with Severe Hypoglycemia	1.4%
Type 2 Diabetes (Single Injection)	
Population	Adults
Population Size	336
Patients with Severe Hypoglycemia	0.9%

Note: These data are from separate clinical trials comparing FIASP® to NovoLog® and Lyumjev to Humalog. These trials did NOT compare FIASP® and Lyumjev head-to-head and no conclusions about safety of these products should be drawn.

Final Question 28 References:

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Complete response to ICR Section I

Q27: Prescribing Information

[REDACTED]

For clarity purposes, Novo Nordisk provides its responses to Section I, "Evidence About Selected Drugs and Their Therapeutic Alternatives Form," including this response, as a complete PDF document. This was uploaded within "Additional Materials for Questions 28".

Novo Nordisk Inc. is providing this summary of information in response to an unsolicited inquiry by CMS. Please see cited references for full discussion of study design and results.

1. Disease Background - Information About Type 1 and Type 2 Diabetes

Diabetes is one of the most prevalent diseases in the United States (U.S.), with 11.3% of people of all ages and 29.2% of adults aged 65 or older currently living with the disease. The Centers for Disease Control and Prevention (CDC) reports that in 2019, 37.1 million Americans had diabetes, with 15.9 million of them aged 65 years or older. Of the 37.1 million Americans with diabetes, 90-95% (33.4 - 35.2 million) are living with type 2 diabetes (T2D) with the remaining 5-10% (1.9 - 3.7 million) suffer from type 1 diabetes (T1D).

Diabetes affects how the body turns food into energy (CDC). In healthy individuals, beta cells (b-cells) in the pancreas release the hormone insulin with each meal to help the body use and/or store the blood glucose (blood sugar) released from digestion of food. For patients with diabetes, the body doesn't make enough insulin and/or doesn't respond to insulin as effectively. Individuals diagnosed with diabetes are either diagnosed with T1D where the pancreas no longer makes insulin or T2D where the body suffers from a combination of inadequate insulin secretion, insulin resistance, and metabolic syndrome.

The absence of insulin production or secretion leads to excess blood sugar staying within the blood. Over time, if diabetes is not properly controlled it can lead to several macrovascular and microvascular complications. The potential microvascular complications include retinopathy causing vision impairment and blindness, nephropathy causing loss of kidney function, and neuropathy causing peripheral nerve damage that can manifest in many ways including loss of limbs and sexual dysfunction. The potential macrovascular complications include cardiovascular disease such as myocardial infarction, stroke, and ischemic disease (Fowler, Michael J.

"Microvascular and Macrovascular Complications of Diabetes." *Clinical Diabetes*, vol. 26, no. 2, 2008, pp. 77–82)

Since insulin production is either completely lost or critically reduced for patients with T1D, insulin replacement therapy is an absolute requirement. Additionally, it is important to note that individuals living with T2D suffer from a progressive disease and these individuals also eventually require insulin therapy to maintain normal glucose levels.

To address the unmet needs of patients requiring insulin therapy, innovation of commercially available insulin products has been necessary since its initial discovery. Before insulin was discovered in 1921, those with T1D died within weeks to years of its onset. The only available treatment was a starvation diet. Bovine and porcine derived insulins were the first commercially available insulin therapy, starting in 1923. However, these first insulin formulations were short acting, requiring patients to take frequent injections, often in the middle of the night, which increases the risk of missing doses. To respond to the unmet need of fewer daily injections, researchers and founders of Novo Nordisk Inc., as well as research teams from Toronto, identified ways to lengthen insulin's duration of action by the mid-1930's. Treatment that avoided the frequent allergic reactions associated with bovine and porcine insulins remained an unmet need until the development of synthetic human insulin in 1978, which became commercially available in 1982.

While synthetic human insulins represented a major development, the need remained for therapies with characteristics that would better imitate the mealtime response of a normal functioning pancreas to mitigate glucose spikes whenever a patient ate a meal. This need led to years of research and the development of faster-acting insulins that keep glucose levels closer to normal around meals. The first of these rapid-acting insulins became broadly available to patients in 1996. Since then, research has continued to further respond to patient needs with multiple innovations achieved, including ultra-rapid acting insulins, which work even faster to better replicate the natural pancreatic insulin response when eating a meal while providing more dosing flexibility to patients compared to previous insulins. Additional innovations include improvements in the insulin delivery systems with the advent of pens which provide an easier and more accurate method of administration, in addition to being less painful, and are more discreet compared with vials and syringes. Substantial evidence demonstrates that insulin pen devices have the potential to improve adherence, enhance quality of life, and reduce the risk of hyperglycemia (Magwire, Melissa L. "Addressing Barriers to Insulin Therapy: The Role of Insulin Pens." *American Journal of Therapeutics*, vol. 18, no. 5, 2011, pp. 392-402).

2. Indications for NovoLog® and FIASP®

a. NovoLog®

Approved in 2000, NovoLog® is a rapid-acting insulin analog containing insulin aspart utilized to improve glycemic control in adults and children with type 1 and T2D (NovoLog® Package Insert). In lay terms, rapid-acting insulins imitate the body's secretion of insulin after a meal, preventing blood sugar spikes that can result in the immediate symptoms of thirst, fatigue, nausea, and blurred vision – and over time cause the serious and long term microvascular and macrovascular complications mentioned earlier. NovoLog® is available as a subcutaneous injection, continuous

subcutaneous infusion (via a pump), or for intravenous use and is available in multiple dosage forms and strengths, and in several different devices depending on a patient's need. See Section 3 for more prescribing information.

b. **FIASP®**

Approved in 2017, FIASP® is a newer insulin formulation with an enhanced rapid-action profile due to a shorter time of onset (FIASP® Package Insert). FIASP® is an ultra-rapid acting insulin analog utilized to improve glycemic control in adults and children with T1D and T2D. FIASP® is a faster-acting insulin aspart due to the addition of vitamin B3 (niacinamide) to increase the speed of initial absorption and an amino acid (L-arginine) to stabilize the formulation. This results in faster absorption with differentiated dosing for use in T1D and T2D. FIASP® appears in the bloodstream faster than NovoLog®; while NovoLog® is approved for use within 5-10 minutes immediately before a meal, FIASP® is approved for use at the start or within 20 minutes after starting a meal. This dosing flexibility provides patients more leeway in their mealtime dosing and was shown to provide better post-prandial (post-meal) glycemic control when compared to NovoLog® in Phase 3 clinical trials.

Failure to follow each product's specific dosing instructions can increase the risk of hypoglycemia. See Section 3 for more prescribing information.

3. Therapeutic Alternatives

The ADA identifies three characteristics of insulins that differentiate them from one another:

- Onset of action: Length of time before insulin reaches blood stream and begins lowering blood glucose
- Peak time: Time during which insulin is at maximum strength
- Duration: Duration of time for which insulin continues to lower blood glucose

There are two main categories of insulin, based on use:

- Basal insulin - Basal insulins are designed to be injected once or twice daily to maintain insulin levels throughout the day and night. The objective of basal insulin is to keep blood sugar levels at goal when one is not eating – but it is not enough to cover glucose spikes after meals.
- Prandial insulin - Prandial insulins have faster onsets and peaks, with shorter durations of action than basal insulins. They are taken around mealtimes to help keep glucose levels closer to normal for meals.

The prandial insulin category is further differentiated into the following sub-categories: short-acting, rapid-acting, and ultra-rapid acting insulins. Prior to addressing what may be appropriate therapeutic alternatives, it is important to note that research and guidelines support the fact that the short-acting insulin sub-category, also referred to as regular human insulin, is not an appropriate therapeutic alternative to NovoLog® or FIASP®. The ADA Standards of Care 2023 differentiate between short-acting and rapid-acting insulin when they state that patients with T1D

should use rapid-acting insulin analogs as they are associated with less hypoglycemia and weight gain as well as lower HbA1c compared with short-acting (human insulins). The guidelines go on to state that the preferred injection insulin regimen for patients with T1D is a long-acting analog with flexible doses of either an ultra-rapid acting analog or rapid-acting analog at meals. Similarly, the American Association of Clinical Endocrinology (AACE) guidelines state that ‘Rapid-acting insulin analogs are preferred over human insulin preparations (e.g., regular insulin) because of their comparatively earlier onset of action’, further underscoring the distinction between the two.

a. Therapeutic Alternatives for NovoLog®

The most “clinically comparable therapeutic alternative” to NovoLog® is Humalog (insulin lispro) and its follow-on biologic ADMELOG (insulin lispro). Humalog is indicated to improve glycemic control in children and adults with both T1D and T2D. ADMELOG is indicated to improve glycemic control in adults and children aged 3 years and older with T1D and adults with T2D.

Prescribing information about NovoLog®, Humalog and ADMELOG is summarized below. Refer to the package inserts for additional information.

Summary of Prescribing Information for NovoLog® and its Therapeutic Alternatives

Selected Drug:

- NovoLog® (Insulin aspart) (Novo Nordisk, Inc.)

Therapeutic Alternatives:

- Humalog (Insulin lispro) (Eli Lilly and Company)
- ADMELOG (Insulin lispro) (Sanofi-Aventis LLC)

Speed of onset/Insulin Type:

- NovoLog®: Rapid-acting
- Humalog: Rapid-acting
- ADMELOG: Rapid-acting

Administration:

- NovoLog®: SC injection, immediately (within 5-10 minutes) prior to the start of a meal, continuous SC infusion (use of insulin pump), intravenous infusion (after dilution and under medical supervision)
- Humalog: SC injection, within 15 minutes before a meal or immediately after a meal, continuous SC infusion (use of insulin pump), intravenous infusion (HUMALOG U-100 only after dilution and under medical supervision)

- ADMELOG: SC injection, within 15 minutes before a meal or immediately after a meal, continuous SC infusion (use of insulin pump), intravenous infusion (after dilution and under medical supervision)

Indications:

- NovoLog®: Improve glycemic control
- Humalog: Improve glycemic control
- ADMELOG: Improve glycemic control

Dosage forms and strengths:

- NovoLog®: Each presentation contains 100 Units of insulin aspart per mL (U-100), available in various devices including vials, PenFill® cartridges, FlexPen®, and FlexTouch®
- Humalog: Injection available in 100 units/mL (U-100) in various devices including vials, KwikPen® prefilled pen, Tempo Penä prefilled pen, KwikPen® prefilled pen, and single-patient-use cartridges and 200 units/mL (U-200) available in KwikPen® prefilled pen
- ADMELOG: Injection available in 100 units/mL (U-100) in various devices including vials and SoloStar® prefilled pens

Populations:

- T1D: NovoLog® (Adults & Children), Humalog (Adults & Children), ADMELOG (Adults and Children 3 years and older)
- T2D: NovoLog® (Adults & Children), Humalog (Adults & Children), ADMELOG (Adults)

b. Therapeutic Alternatives For FIASP®

The most “clinically comparable therapeutic alternative” to FIASP® is Lyumjev (insulin lispro-aabc). Lyumjev is indicated to improve glycemic control in children and adults with T1D and T2D. Prescribing information about FIASP® and Lyumjev, is detailed below. Refer to the package inserts for additional information.

Summary of Prescribing Information for FIASP® and its Therapeutic Alternatives

Selected Drug

- FIASP® (Ultra-rapid acting insulin aspart)

Therapeutic Alternative:

- Lyumjev (Insulin lispro-aabc) (Eli Lilly and Company “LYUMJEV PI”)

Speed of onset/Insulin Type:

- FIASP: Faster rapid-acting

- Lyumjev: Faster rapid-acting

Administration:

- FIASP®: Subcutaneous injection, start of a meal or within 20 minutes after starting a meal, continuous SC infusion (use of insulin pump), intravenous infusion (after dilution and under medical supervision)
- Lyumjev: Subcutaneous injection, start of a meal or within 20 minutes after starting a meal, LYUMJEV U-100 only by use of insulin pump, intravenous infusion (LYUMJEV U-100 only after dilution and under medical supervision)

Indications:

- FIASP®: Improve glycemic control
- Lyumjev: Improve glycemic control

Dosage forms and strengths:

- FIASP®: Injection available in 100 units/mL (U-100) and various formats, including multiple-dose vial, FIASP® FlexTouch® pen, PenFill® cartridges for use in a PenFill® cartridge device, and PumpCart® cartridges for use in a compatible insulin pump.
- Lyumjev: Injection available in 100 units/mL (U-100) and various formats, including vial, KwikPen®, Tempo Pen®, and single-patient-use cartridges.

Populations:

- T1D:
 - FIASP®: Adults & Children
 - Lyumjev: Adults & Children
- T2D:
 - FIASP®: Adults & Children
 - Lyumjev: Adults & Children

4. Guideline Recommendations in Course of Care: NovoLog® and FIASP®

a. Importance of Assessing Glycemic Control

Glycemic control is assessed by HbA1c measurement, continuous glucose monitoring (CGM), and blood glucose monitoring (BGM). HbA1c is the metric used to date in clinical trials demonstrating the benefits of improved glycemic control. Individual glucose monitoring is a useful tool for diabetes self-management, which includes meals, physical activity, and medication adjustment, particularly in individuals taking insulin. According to 2023 ADA guidelines, HbA1c alone does not provide a measure of glycemic variability, fluctuations in blood glucose levels

throughout the day, or hypoglycemia. For patients prone to glycemic variability, especially people with T1D or T2D with severe insulin deficiency, glycemic control is best evaluated by the combination of results from BGM and HbA1c measurement.

b. T1D Treatment Guidelines Specific to Rapid-Acting Insulins

The ADA Standards of Care recommend the use rapid-acting insulins (prandial insulins) in T1D as follows:

“Most individuals with T1D should use rapid-acting insulin analogs to reduce hypoglycemia risk.”

- Rapid-acting insulin analogs are associated with less hypoglycemia and weight gain as well as lower HbA1c compared with short-acting (human insulins).
- Ultra-rapid acting insulins may reduce prandial excursions better than rapid-acting analogs.

“Most individuals with T1D should be treated with multiple daily injections of prandial and basal insulin, or continuous subcutaneous insulin infusion.”

- The optimal time to administer prandial insulin varies, based on the pharmacokinetics of the formulation, the premeal blood glucose level, and carbohydrate consumption.
- The preferred injection insulin regimen for patients with T1D is taking a long-acting analog with flexible doses of an ultra-rapid acting analog or rapid-acting analog at meals.

c. T2D Treatment Guidelines Specific to Rapid-Acting Insulins

The ADA Standards of Care also recommend the use of rapid-acting insulins (prandial insulins) in T2D as an add-on to a GLP-1 RA to reach glycemic targets as follows:

- “Many individuals with T2D require doses of insulin before meals, in addition to basal insulin, to reach glycemic targets.”

“If the individual is not already being treated with a GLP-1 RA, a GLP-1 RA (either in free combination or fixed-ratio combination) should be considered prior to prandial insulin...”. “For individuals who advance to prandial insulin, a prandial insulin dose of 4 units or 10% of the amount of basal insulin at the largest meal or the meal with the greatest post-prandial excursion is a safe estimate for initiating therapy. The prandial insulin regimen can then be intensified based on individual needs.”

d. Considerations for NovoLog® and FIASP® Based on Modes of Administration

The 2023 ADA Standards of Care recognize the value of flexible modes of administration of rapid-acting insulins brought about by insulin pens and pumps and make the following recommendations:

“For people with insulin-requiring diabetes on multiple daily injections, insulin pens are preferred *[to syringes]* in most cases”.

“Automated insulin delivery systems *[including pumps]* should be offered for diabetes management to youth and adults with T1D who are capable of using the device safely”.

Insulin pump therapy can be offered for diabetes management to youth and adults on multiple daily injections with T2D who are capable of using the device safely.

Innovation in prandial insulin and the ways in which it is administered have helped address many of the unmet needs for patients living with diabetes, such as post-prandial glucose control, overcoming restrictions on daily physical activities, and improvement in patient experience. An independent, online survey of adults with T1D, and parents and physicians of children with T1D found that 91% of adults and 97% of parents experienced at least one major challenge with mealtime insulin dosing (Fowler, Michael J. "Microvascular and Macrovascular Complications of Diabetes." *Clinical Diabetes*, vol. 26, no. 2, 2008, pp. 77–82.) Novo Nordisk Inc.'s responses to Questions 28-32 will demonstrate that the evolution of prandial insulin from short-acting (human) to rapid-acting to ultra-rapid acting has not only improved post-prandial glucose control in patients, but also helped address their disease burden through more flexible dosing and improved modes of administration.

Q28: Therapeutic Impact and Comparative Effectiveness

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For clarity purposes, Novo Nordisk provides its responses to Section I, “Evidence About Selected Drugs and Their Therapeutic Alternatives Form,” including this response, as a complete PDF document. This was uploaded within “Additional Materials for Questions 28”.

Novo Nordisk Inc. is providing this summary of information in response to an unsolicited inquiry by CMS. Please see cited references for full discussion of study design and results.

1. Description of Important Outcomes for Evaluating Insulin Treatments

Accepted outcomes for evaluating insulins as a pharmacologic treatment for patients living with diabetes are as follows:

a. Hemoglobin A1C

The Hemoglobin A1c (HbA1c) measurement is an indicator of a patients’ average glucose control over the prior three months and whether their desired glycemic targets have been achieved. Change in HbA1c from baseline is the most common metric in clinical trials and other studies to demonstrate improved glycemic control [1].

b. Post-Prandial Glucose

Post-prandial glucose (PPG) measures the glucose level achieved at the time of testing after a meal is consumed. This is typically assessed one or two hours after the meal. Elevated PPG levels may be associated with adverse outcomes, and it is recommended that PPG levels be monitored in individuals when their pre-meal glucose values are within target range, but HbA1c values are above target [1].

c. Safety (Hypoglycemia)

The key safety concern associated with insulin injectables is hypoglycemia (low blood sugar). In general, patients with both type 1 diabetes (T1D) and type 2 diabetes (T2D) must ensure that they do not take more insulin than needed, which may cause hypoglycemia and in severe cases, can lead to unconsciousness, seizures, and brain function impairment [2]. Nocturnal hypoglycemia is a type of hypoglycemia that tends to occur if a patient does not eat enough food after taking an insulin dose or taking more insulin than prescribed in the evening [3].

In the sections that follow, we will present effectiveness and safety data for NovoLog® and its therapeutic alternative Humalog. We will not present any data for ADMELOG, as it is a follow-on biologic of Humalog (same active ingredient - insulin lispro) and is expected to have the same effectiveness and safety profile. The safety and effectiveness of ADMELOG have been established in clinical studies in adult patients with T1D and T2D and is based on adequate and well controlled studies of ‘another insulin lispro product’ in adult and pediatric patients 3 years of age and older with T1D and adult patients with T2D [4].

2. Clinical Outcomes of NovoLog®

Key Takeaways

- The comparator group in Phase 3 clinical trial programs for rapid-acting NovoLog® and Humalog was regular human insulin, also referred to as short-acting, because it was the only prandial insulin available when these Phase 3 programs were designed.
- NovoLog® and Humalog Phase 3 clinical trials were structured to be treat-to-target, which means the overall HbA1c reductions are expected to be the same across treatment groups.
- NovoLog® and Humalog were found to be non-inferior to regular human insulin on HbA1c and hypoglycemia outcomes in T1D and T2D.
- NovoLog® is superior to regular human insulin on PPG levels achieved after mealtime in T1D patients.

The Phase 3 Clinical Trial programs for NovoLog® and Humalog used regular human insulin as their active comparator [2], [5]. For the NovoLog® clinical trial program, regular human insulin was chosen as the active comparator because it was the only prandial insulin available when the Phase 3 program was designed. Humalog was the first rapid-acting human insulin analog available on the market and did not receive FDA approval nor become commercially available until 1996, which was after the development and initial implementation of the NovoLog® Phase 3a clinical trial program.

Note: There is no pivotal head-to-head trial comparing efficacy or safety of NovoLog® with Humalog, so no direct comparative effectiveness statements can be made from these studies.

a. Effectiveness of NovoLog® and Humalog

HbA1c

As per U.S. Food and Drug Administration (FDA) directive, clinical development program for NovoLog® used non-inferiority for change in HbA1c as the primary endpoint [6]. It is important to note that due to FDA guidance the programs were designed as treat-to-target trials where insulin doses in both comparator and investigational arms are titrated to achieve a known and validated target level for glycemic control [6]. For this reason, overall HbA1c reductions in treat-to-target studies are expected to be the same among treatment groups, with no differences in efficacy expected [7].

Table 1 summarizes HbA1c results for each product's pivotal trials when administered as a subcutaneous daily injection [2], [5]. NovoLog® and Humalog were found to be non-inferior to regular human insulin on change in HbA1c in T1D and T2D.

Table 1. NovoLog® and Humalog HbA1c Pivotal Trial Results: Subcutaneous Daily Injections

Characteristic	NovoLog®
Type 1 Diabetes	
Population	Adults
Rapid Acting Insulin Cohort Arm (N)	596
Mean Baseline HbA1c	7.9
Mean Change from Baseline HbA1c	-0.1
Type 2 Diabetes	
Population	Adults
Population Size	90
Mean Baseline HbA1c	8.1
Mean Change from Baseline HbA1c	-0.3
Characteristic	Humalog
Type 1 Diabetes	
Population	Adults & Adolescents
Rapid Acting Insulin Cohort Arm (N)	81
Mean Baseline HbA1c	8.2
Mean Change from Baseline HbA1c	-0.1
Type 2 Diabetes	
Population	Adults
Population Size	722
Mean Baseline HbA1c	8.2
Mean Change from Baseline HbA1c	-0.7

Note: These data are from separate clinical trials comparing NovoLog® to regular human Insulins and Humalog to regular human insulins. These trials did NOT compare NovoLog® and Humalog head-to-head and no conclusions about comparative effectiveness of NovoLog® and Humalog should be drawn.

Two open-label, parallel design pivotal trials compared NovoLog® to buffered regular human insulin (Velosulin) in adults with T1D receiving a subcutaneous infusion with an external insulin pump. The two treatment regimens had comparable changes in HbA1c [2].

Post-Prandial Glucose

In the NovoLog® T1D pivotal trial, mean PPG levels (mg/dl ± SEM) were significantly lower for subjects in the NovoLog® group compared with the regular human insulin group after breakfast (156 ± 3.4 vs. 185 ± 4.7), lunch (137 ± 3.1 vs. 162 ± 4.1), and dinner (153 ± 3.1 vs. 168 ± 4.1), when assessed after 6 months of treatment [8]. These data show that the patients taking NovoLog® did not experience significant spikes in their blood glucose readings after a meal compared to those taking regular human insulin.

b. Safety of NovoLog® and Humalog

Hypoglycemia

In both of their Phase 3 Clinical Trial programs, NovoLog® and Humalog were compared with regular human insulins (please see above for explanation). In this section we will provide the hypoglycemia results from those clinical trials. In NovoLog® trials, severe hypoglycemia was defined as hypoglycemia for which patients could not self-treat (i.e., required the assistance of another person or hospitalization) [2].

Table 2 shows rates of severe hypoglycemia observed in pivotal trials of rapid-acting insulins. The severe hypoglycemia rates for NovoLog® and Humalog were similar to regular human insulin [2], [5].

Table 2. Hypoglycemia Rates in Pivotal Trials of NovoLog® and Humalog: Subcutaneous Daily Injections

Characteristic	NovoLog®
Type 1 Diabetes	
Population	Adults
Population Size	596
Patients with Severe Hypoglycemia	17%
Type 2 Diabetes	

Population	Adults
Population Size	90
Patients with Severe Hypoglycemia	10%
Characteristic	Humalog
Type 1 Diabetes	
Population	Adults & Adolescents
Population Size	81
Patients with Severe Hypoglycemia	17%
Type 2 Diabetes	
Population	Adults
Population Size	722
Patients with Severe Hypoglycemia	2%

Note: These data are from separate clinical trials comparing NovoLog® to regular human insulins and Humalog to regular human insulins. These trials did NOT compare NovoLog® and Humalog head-to-head and no conclusions about safety of NovoLog® and Humalog should be drawn.

3. Clinical Outcomes of FIASP®

Key Takeaways

- **FIASP® and Lyumjev Phase 3 clinical trials presented in this section were treat-to-target, which means the overall HbA1c reductions are expected to be the same across treatment groups.**
- **In general, FIASP® shows non-inferiority to NovoLog® and Lyumjev shows non-inferiority to Humalog in their ability to lower HbA1c and in hypoglycemia rates in T1D and T2D, although some evidence points to greater efficacy and lower hypoglycemia rates with FIASP®.**
- **FIASP® outperforms NovoLog® and Lyumjev outperforms Humalog in terms of reducing 1-hour PPG increments in patients with T1D and T2D.**

The Phase 3 Clinical Trial program for FIASP® used NovoLog® as its active comparator while the program for Lyumjev used Humalog as its active comparator. FIASP® was developed to achieve a faster onset of action than currently available rapid acting insulin analogs. NovoLog® was applied as the active comparator for FIASP® to confirm its clinical efficacy and safety, which

at the time was one of the most broadly used prandial insulins on the US market and thus reflective of the current standard of care. FIASP® pivotal trials were conducted to test non-inferiority with NovoLog® while Lyumjev’s pivotal trials included comparisons with Humalog when administered via subcutaneous daily injection and continuous subcutaneous infusion in adults with T1D and T2D [9] [10]. These trials are summarized below by HbA1c, PPG, and hypoglycemia.

Note: There is no pivotal head-to-head trial comparing efficacy of FIASP® with Lyumjev, so no direct comparative effectiveness statements can be made from these studies.

a. Effectiveness of FIASP® and Lyumjev

HbA1c

Once again it is important to note that all studies were treat-to-target where insulin doses are titrated to enable patients to achieve a known and validated target level of glycemic control. For this reason, overall HbA1c reductions in treat-to-target studies are expected to be the same among treatment groups, with no differences in efficacy expected [7].

Once again, as per FDA directive, clinical development program for FIASP® used non-inferiority for change in HbA1c as the primary endpoint [6]. It is important to note that due to FDA guidance the programs were designed as treat-to-target trials where insulin doses in both comparator and investigational arms are titrated to achieve a known and validated target level for glycemic control [6]. For this reason, overall HbA1c reductions in treat-to-target studies are expected to be the same among treatment groups, with no differences in efficacy expected [7].

Four pivotal, treat-to-target, non-inferiority clinical trials were performed on FIASP® (subcutaneous injection) in adults: two trials in patients with T1D and two in patients with T2D [11] [12] [13] [14]. FIASP® demonstrated non-inferiority in HbA1c reduction compared to NovoLog® in patients with T1D (ONSET 8 [11]) and T2D (ONSET 2 [13] and 9 [14]). One trial in patients with T1D (ONSET 1) showed that mealtime FIASP® significantly reduced HbA1c versus NovoLog® ($p = 0.0003$) [12]. Lyumjev demonstrated non-inferiority with Humalog in adults with both T1D and T2D [15] [16].

Table 3 summarizes HbA1c results from each product’s respective pivotal trials when administered via subcutaneous daily injections [9] [10].

Table 3. FIASP® and Lyumjev HbA1c Pivotal Trial Results: Subcutaneous Daily Injections

Characteristic	Mealtime FIASP®
Type 1 Diabetes	
Population	Adults (ONSET 1)
Population Size	381

Mean Baseline HbA1c	7.6
Mean Change from Baseline HbA1c	-0.32
Type 2 Diabetes	
Population	Adults (ONSET 2)
Population Size	345
Mean Baseline HbA1c	8.0
Mean Change from Baseline HbA1c	-1.38
Characteristic	Mealtime Lyumjev
Type 1 Diabetes	
Population	Adults
Population Size	451
Mean Baseline HbA1c	7.3
Mean Change from Baseline HbA1c	-0.12
Type 2 Diabetes	
Population	Adults
Population Size	336
Mean Baseline HbA1c	7.3
Mean Change from Baseline HbA1c	-0.36

Note: These data are from separate clinical trials comparing FIASP® to NovoLog® and Lyumjev to Humalog. These trials did NOT compare FIASP® and Lyumjev head-to-head and no conclusions about comparative effectiveness of these products should be drawn.

Pivotal trials for FIASP® and Lyumjev were also conducted for continuous subcutaneous infusion administration in patients with T1D [9], [10], [17]. Both FIASP® and Lyumjev were found to be non-inferior to NovoLog® and Humalog, respectively. Results for mean change from baseline HbA1c for FIASP® and Lyumjev are summarized in Table 4 below.

Post-prandial Glucose

Furthermore, all FIASP® trials revealed that mealtime administration of FIASP® outperformed NovoLog® in terms of reducing 1-hour PPG increments (p<0.05 in all studies) [11] [12] [13] [14].

Similarly, significantly lower 1-hour PPG excursions were reported with Lyumjev compared to Humalog [15] [16].

b. Safety of FIASP® and Lyumjev

Hypoglycemia

As with all insulin products, the most common adverse event with FIASP® is hypoglycemia. In NovoLog® pivotal trials, severe hypoglycemia was defined as an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. 9]. Safety profiles and overall rates of severe or blood glucose-confirmed hypoglycemia were mostly similar between FIASP® and NovoLog® in most pivotal studies [11] [12] [13] [17]. A multicenter trial in adults with T2D found a lower relative risk of severe hypoglycemia for FIASP® compared to NovoLog® (RR: 0.81; p = 0.019) [14].

Table 4 summarizes the safety profile of FIASP® and Lyumjev studied in their respective pivotal trials [9] [10].

Table 4. Hypoglycemia Rates in Pivotal Trials of FIASP® and Lyumjev

Characteristic	Mealtime FIASP®
Type 1 Diabetes (Single Injection)	
Population	Adults
Population Size	386
Patients with Severe Hypoglycemia	6.7%
Type 1 Diabetes (Continuous Subcutaneous Infusion)	
Population	Adults
Population Size	236
Patients with Severe Hypoglycemia	4.7%
Type 2 Diabetes (Single Injection)	
Population	Adults
Population Size	341
Patients with Severe Hypoglycemia	3.2%
Characteristic	Mealtime Lyumjev
Type 1 Diabetes (Single Injection)	
Population	Adults

Population Size	451
Patients with Severe Hypoglycemia	5.5%
Type 1 Diabetes (Continuous Subcutaneous Infusion)	
Population	Adults
Population Size	215
Patients with Severe Hypoglycemia	1.4%
Type 2 Diabetes (Single Injection)	
Population	Adults
Population Size	336
Patients with Severe Hypoglycemia	0.9%

Note: These data are from separate clinical trials comparing FIASP® to NovoLog® and Lyumjev to Humalog. These trials did NOT compare FIASP® and Lyumjev head-to-head and no conclusions about safety of these products should be drawn.

4. Beyond Clinical Outcomes – Improving Patient Experience

Key Takeaways

- **The introduction of novel delivery systems, including pens and pumps, represented a key advancement in diabetes care for patients.**
- **In addition to improved treatment satisfaction, quality of life, and adherence, insulin pens offer safety related to dosing accuracy compared to vials/syringes.**
- **A 16-week, open-label, single arm study showed that patients using insulin pumps preferred using NovoLog® over Humalog.**

Diabetes is a multi-faceted chronic condition for which treatment success goes beyond clinical outcomes and depends on patient satisfaction, acceptance, adherence, and quality of life. Diabetes has a high treatment burden wherein patients are required to undertake strict self-management and adhere to their treatment protocols at the cost of their quality of life. From this standpoint, the introduction of the pen delivery system represented a key advancement in diabetes care for patients [18].

Both NovoLog® and FIASP® are available in pen devices in addition to vials. Insulin pens have several advantages over the vial/syringe method of insulin delivery, including improved patient satisfaction and adherence, greater ease of use, superior accuracy for delivering small doses of insulin, greater social acceptability, and less reported injection-site pain [19]. Beyond the impact on patient satisfaction and quality of life, patient safety related to dosing accuracy is better with the use of insulin pens versus the vial/syringe method [20]. Patients using vial/syringe are at

greater risk of drawing up an incorrect insulin dose, with an estimated relative error of 19%, which is a significant risk and concern [21]. An open-label, randomized, crossover study showed that 73% of patients felt more confident in the accuracy of the insulin dose delivered with the pen while a separate study evaluating patient satisfaction associated with the method of insulin administration found that those using pens were more likely to adhere to their insulin therapy, resulting in fewer hypoglycemic episodes and reduced healthcare costs [21], [22].

For people living with diabetes who find injections difficult, an insulin pump can bring welcome relief. Insulin pumps are small, computerized devices that deliver prandial insulin as a surge ("bolus") dose, at the patient's direction, around mealtime. This delivery mimics the body's normal release of insulin and can integrate with the patient's continuous glucose monitor, thereby improving convenience, satisfaction, and treatment adherence. A 16-week, open-label, single arm study was conducted to compare the use of NovoLog® via continuous subcutaneous infusion in 513 adults with either T1D or T2D who previously used Humalog [23]. This study reported average overall Insulin Treatment Satisfaction Questionnaire (ITSQ) scores for NovoLog® were significantly greater than for Humalog (82.9 vs. 81.2; $p < 0.001$) [23]. This was driven by subjects feeling less bothered by symptoms of low blood sugar, less worried about experiencing low blood sugar episodes during the night, more satisfied with the stability of their blood sugar levels, and more pleased with their level of blood sugar control. In addition, subjects believed that NovoLog® therapy was less time consuming and less burdensome to manage than their previous experience with Humalog. Furthermore, subjects using NovoLog® had less of a tendency to feel down or depressed and had more favorable perceptions of pain and physical discomfort [23].

5. Healthcare Resource Use

Several studies quantify the direct and indirect costs of diabetes in the U.S. and how successful control of the disease can offset these costs. An ADA-commissioned study (2018) estimated the national cost of diabetes at \$327 billion, 73% of which was driven by direct healthcare expenditures attributed to diabetes and 27% driven by lost productivity from work-related absenteeism, reduced productivity, unemployment, and premature mortality [24]. People with diabetes incurred 24.8% of U.S. hospital inpatient days, 13.9% of which were specifically attributed to a diagnosis of diabetes. People with diabetes represent an even higher percentage of nursing/residential facility days (26.1% of the total incurred by the U.S. population in 2016) and incurred high percentages for physician office visits (21.5%), emergency department visits (12.2%), hospital outpatient visits (19.2%), and home health visits (21.2%). Also, approximately 61% of healthcare expenditures attributed to diabetes are used by populations older than 65 years, much of which is associated with vascular complications including cardiovascular-related care.

There is robust evidence linking high PPG levels with the development of vascular complications [25]. The Diabetes Control and Complications Trial (DCCT) showed definitively that better glycemic control in patients with T1D is associated with 50-76% reduction in rates of development and progression of microvascular complications such as retinopathy, neuropathy, and diabetic kidney disease [26]. Insulin therapies that control prandial glucose, like NovoLog® and FIASP®,

can offset health-related resource utilization that would otherwise be incurred by vascular complications linked with high PPG levels [27].

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Q29: Comparative Effectiveness in Specific Populations

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For clarity purposes, Novo Nordisk provides its responses to Section I, “Evidence About Selected Drugs and Their Therapeutic Alternatives Form,” including this response, as a complete PDF document. This was uploaded within “Additional Materials for Questions 28”.

Novo Nordisk Inc. is providing this summary of information in response to an unsolicited inquiry by CMS. Please see cited references for full discussion of study design and results.

In our responses to Q27 and Q28 we have outlined evidence for NovoLog® and FIASP® as well as their therapeutic alternatives in adults with type 1 diabetes (T1D) and type 2 diabetes (T2D).

In the sections below, we discuss evidence relevant for specific subpopulations – pediatric patients, older adults, and patients with renal impairment. We will then touch on innovations in delivery methods for insulin - pens and pumps - and their benefits in specific subpopulations.

1. Pediatric Patients

Key Takeaways

- **NovoLog® and Humalog are non-inferior to regular human insulin in HbA1c reduction and hypoglycemia rates in pediatric patients with T1D. However, continuous subcutaneous infusion of NovoLog® outperforms Humalog in achieving age-specific American Diabetes Association (ADA) recommended HbA1c goals in these patients.**
- **Not only is FIASP® non-inferior to NovoLog® in terms of HbA1c outcomes and hypoglycemia rates, but it also offers improved flexibility, as it can be administered post-meal with similar efficacy results as mealtime FIASP®. Elevated post-prandial glucose levels may be associated with long term complications.**

As a reminder, the Phase 3 Clinical Trial programs for NovoLog® and Humalog used regular human insulin as their active comparator [1], [2]. For the NovoLog® clinical trial program, regular human insulin was chosen as the active comparator because it was the only prandial insulin available when the Phase 3 program was designed. Humalog was the first rapid-acting human insulin analog available on the market and did not receive FDA approval nor become commercially available until 1996, which was after the development and initial implementation of the NovoLog® Phase 3a clinical trial program.

a. Clinical Effectiveness and Safety of NovoLog®

Both NovoLog® and Humalog are indicated to improve glycemic control in children with T1D and T2D.

Pivotal trials of NovoLog® and Humalog indicate that they are non-inferior to regular human insulin in reducing HbA1c from baseline [1], [2]. In a 24-week, parallel-group study of pediatric patients with T1D aged 6-18 years, subcutaneous injection of NovoLog® achieved glycemic control comparable to regular human insulin, as measured by change in HbA1c [1]. Similar results were seen in another trial in children with T1D (n=26) aged 2 to 6 years [1]. However, a 2008 randomized clinical trial of 298 pediatric patients with T1D using continuous subcutaneous infusions found that NovoLog® outperformed Humalog in achievement of age-specific ADA recommended HbA1c goals (NovoLog®, 59.7% vs Humalog, 43.8%, P=0.040) [3]. These trials also report comparable hypoglycemia rates between NovoLog® and regular human insulin, and Humalog and regular human insulin.

b. Clinical Effectiveness and Safety of FIASP®

Unpredictable eating habits of children with T1D is a significant problem that parents need to account for when considering insulin treatment. It can be difficult to determine the amount of food a child will eat, thereby complicating insulin dosing decisions before mealtime [4]. The ability to inject FIASP® post-prandially (after a meal) provides flexibility to address this concern helping to keep children within the target glycemic level with less risk for excursions. Over the life of the child, this can be an important contributor of long-term benefit and help delay disease progression.

A randomized controlled trial of children aged 2 to 17 years with T1D found that at week 26, mealtime and post meal FIASP® were non-inferior to NovoLog® in terms of HbA1c change from baseline [5]. Change from baseline in 1-hour postprandial glucose significantly favored mealtime FIASP® versus NovoLog® at breakfast, main evening meal, and over all meals ($P < 0.01$ for all) [5]. No statistically significant differences in hypoglycemia rates were observed. Additionally, there was no significant difference in mean self-measured blood glucose for post-meal FIASP® versus mealtime FIASP® [5]. The overall rate of severe hypoglycemic episodes was comparable between post-meal and mealtime FIASP® (1.11 [95% CI 0.90 - 1.37]) [5]. These results indicate that there is improved flexibility with FIASP® administration, as it can be administered post-meal with similar efficacy results.

In summary, FIASP® has the flexibility to be dosed at the start of a meal or within 20 minutes after starting the meal, giving parents a more reliable and user-friendly treatment to help manage their child's diabetes [6].

2. Older Adults (65+)

Key Takeaways

- **Older adults (aged 65+) - a demographic with a higher rate of T2D and higher rates of serious co-morbidities - were well-represented in Novo Nordisk Inc.'s clinical trials and safety and effectiveness of NovoLog® and FIASP® were consistent in these patients.**

a. Epidemiology and Importance of Insulins in Older Adults

More than 1 in 4 adults over the age of 65 years have diabetes. While most older adults have T2D, this dynamic is rapidly changing due to improved survival of adults living with T1D [7]. Older adults with diabetes have higher rates of premature death, functional disability, muscle loss, and comorbidities (including hypertension, coronary heart disease, and stroke) compared to those without diabetes [8]. Diabetes care for older adults is complicated by the presence of common geriatric syndromes that can impede individuals' ability to self-manage their disease (e.g., frailty, cognitive impairment, depression). At the same time, hypoglycemic events have been linked to increased risk of dementia and cognitive decline [9]. Older adults diagnosed with diabetes are also at increased risk for other geriatric-related conditions, such as falls and osteoporosis [9].

b. Effectiveness and safety in older adults

NovoLog®'s pivotal trials included an assessment of efficacy in geriatric populations. Of the total number of patients (n=1,375) treated with NovoLog® in three controlled clinical studies, 2.6% (n=36) were 65 years of age or older. Half of these patients had T1D and the other half had T2D. The HbA1c response to NovoLog® did not differ by age in these trials [1]. The pharmacokinetic and pharmacodynamic properties of NovoLog® and regular human insulin were investigated in a single dose study in 18 subjects with T2D who were ≥ 65 years of age. The relative differences in pharmacokinetics and pharmacodynamics in geriatric patients with T2D between NovoLog® and regular human insulin were similar to those in younger adults indicating that it has a similar effect in this population as it does in adults [1].

Similarly, in three controlled clinical studies, 192 of 1,219 (16%) FIASP®-treated patients with T1D or T2D were 65 years or older and 24 (2%) were 75 years or older [6]. The trials found consistent safety and effectiveness results between these elderly patients and younger adults [6].

3. Renal Impairment

Key Takeaways

- **Lowering blood glucose delays the onset and progression of kidney damage**
- **Renal impairment does not affect the pharmacokinetics of NovoLog® or FIASP®, thereby enabling their use in this population.**

The ADA estimates that approximately 20–40% of people with diabetes will develop diabetic chronic kidney disease (CKD) [10]. The presence of CKD significantly increases cardiovascular risks: almost half of patients with CKD stage 4 and 5 develop cardiovascular disease [11]. CKD can progress to end-stage renal disease (ESRD), which requires dialysis or kidney transplantation, reduces quality of life, and can lead to premature mortality [12]. Large, randomized studies have shown that lowering blood glucose delays the onset and progression of kidney damage as measured by urinary albumin excretion and estimated glomerular filtration rate [10], (DCCT). In patients with CKD, a reduction in clearance rates may present dosing challenges for any medications ingested and cleared in the kidneys, as the resultant prolonged duration of these medications in the bloodstream could have unanticipated adverse effects. Since NovoLog® and FIASP® are recognized for their rapid onset and shorter duration, this may mitigate these

concerns [14]. Furthermore, a study assessing the effects of a single dose of NovoLog® in patients with comorbidities, including patients with diabetes and renal impairment, found that renal impairment does not affect the pharmacokinetics of NovoLog® in a clinically significant manner [15]. Thus, NovoLog® and FIASP® are effective treatment strategies in this population of CKD patients with T1D and T2D.

4 - Common Methods of Administration and Their Benefits in Specific Subpopulations

Key Takeaways

- **Patient safety related to dosing accuracy is better with the use of insulin pens versus the vial/syringe method.**
- **85% of patients reported they found it easier to read the insulin dose scale with a pen compared with a vial and syringe.**
- **A significantly greater percentage of patients were adherent after switching to an insulin pen (54.6% versus 36.1%, $p < 0.01$) and the likelihood of hypoglycemic events was reduced by 50%.**

a. Administration by vial and syringe

Traditionally, insulin is provided in a vial and administered via a syringe, which presents a series of challenges. For some, the vial/syringe can be disruptive and draining, and it can also be associated with anxiety from pain or fear associated with the needles, and the fear of social stigma around the use of syringes [16]. Also, multiple comorbidities such as dementia, vision loss, neuropathies, poor mobility, and poor manual dexterity can affect the patient's ability to self-inject insulin especially in the elderly population [17].

b. Novo Nordisk Inc. introduces first insulin pen

Given the challenges of administering insulin by vial and syringe, Novo Nordisk Inc. invested in the development of innovative delivery methods for its insulins and continues to do so. Novo Nordisk Inc. launched the very first insulin pen (NovoPen®) in 1985 [18] and has continued to improve their functionality to better meet patient needs (e.g., NovoLog® FlexPen®, FIASP® FlexTouch®, NovoPen Echo®) [19], [20], [21].

Patient safety related to dosing accuracy is better with the use of insulin pens versus the vial/syringe method [22]. Patients using vial/syringe are at greater risk of drawing up an incorrect insulin dose, with an estimated relative error of 19% in dosing accuracy, which is a significant risk and concern for the elderly [17]. By contrast, pens have a dial that is turned to select the correct dose (no reading of a syringe required) and the device clicks as the patient selects each unit [20], which helps individuals with impaired vision or dexterity problems select the correct dose [23], [17]. In an open-label randomized crossover study, 85% of patients reported that they found it easier to read the insulin dose scale with the pen compared with the vial/syringe [24]. Seventy-three percent (73%) of patients in the study felt more confident in the accuracy of the insulin dose delivered with the pen, compared with 19% for the vial/syringe [24]. A large review specific to

studies in the elderly population found that the ability to dial up a dose in a pen led to higher accuracy and reliability than syringe dosing, particularly for lower doses often used by the elderly [17]. Additionally, the compact, portable, and easy to grip structure of pens benefits those with manual dexterity impairments, while the less painful injections and overall ease of use likely contribute to patient preference for insulin pens [17].

A study evaluating patient satisfaction associated with the method of insulin administration found that those using pens reported more comfort and confidence with their device and were thus more likely to adhere to their insulin therapy, resulting in fewer hypoglycemic episodes and reduced healthcare costs [25]. Additionally, a retrospective claims analysis of 1156 patients with T2D examined the association of insulin delivery method and adherence by examining outcomes before and after switching to an insulin analog pen [26]. A significantly greater percentage of patients were adherent after switching to the pen device (54.6% versus 36.1%, $p < 0.01$) and the likelihood of hypoglycemic events was reduced by 50% after switching to an insulin pen (Odds ratio = 0.50; 95% Confidence interval, 0.37–0.68; $p < 0.05$) [26]. This is an important consideration in the elderly population where adherence is negatively impacted by multimorbidity, cognitive impairment, and complex medication regimens [27]. Additionally, adjusted mean annual diabetes-related and all-cause healthcare costs per patient significantly decreased after switching to the insulin pen (\$16,359 to \$14,769; $p < 0.01$, and \$1,415 to \$627; $p < 0.01$, respectively) [26]. Thus, Novo Nordisk Inc.'s innovation in insulin delivery methods has filled a significant unmet need in patients with T1D and T2D, especially in specific subpopulations like older adults who can benefit from ease of administration of their medications.

c. Insulin pumps

Advancements in the development of modern insulin including rapid-acting analogs have spurred progress in insulin delivery devices and glucose monitoring technology [28]. One of these advancements is insulin pumps with rapid-acting insulin formulations which are mainly used by individuals living with T1D, although 10% of pump users live with T2D [29]. The use of insulin pumps has increased dramatically in the United States from <7,000 users in 1990 to nearly 100,000 in 2000 and >350,000 in 2022 [30]. There are many advantages to using an insulin pump compared to individual subcutaneous injections from which pediatric and elderly patients benefit, including precision, flexibility, and convenience.

1. Insulin pump therapy allows for more precise dosing which ultimately leads to improved outcomes. Many studies and systematic reviews have demonstrated improved glycemic control and a reduction in hypoglycemia with insulin pump therapy compared to injections in pediatric and adult populations living with T1D [31], [32], [33], [34], [35], [36], [37], [38].
2. Insulin pumps continuously deliver insulin instead of requiring a patient to inject separate injections for their basal insulin and mealtime insulin. Additionally, anytime changes in insulin dosing are needed, either the basal and/or mealtime component doses can easily be programmed into the pump which then begins administering new doses immediately, while those using injections must manually adjust to each new regimen. Thus, pump

therapy allows for increased flexibility, especially when outside the home, which is especially important for pediatric patients.

3. Where injections require administration (injection under the skin) before each meal or snack, a push of a button can deliver prandial insulin via pumps, thereby offering patients an alternative with fewer daily injections. This is a very important advantage not only in adults, but also pediatric and elderly patients.

In summary, Novo Nordisk Inc.'s investment in novel delivery systems has enabled improved patient experience in specific subpopulations such as pediatric and elderly patients. Newer methods of insulin administration offer several advantages to these specific subpopulations which can improve clinical outcomes in these patients.

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Q30: Addressing Unmet Medical Needs

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

For clarity purposes, Novo Nordisk provides its responses to Section I, “Evidence About Selected Drugs and Their Therapeutic Alternatives Form,” including this response, as a complete PDF document uploaded within “Additional Materials for Questions 28”.

Novo Nordisk Inc. is providing this summary of information in response to an unsolicited inquiry by CMS. Please see cited references for full discussion of study design and results.

Rapid-acting insulin analogs including NovoLog® and FIASP® address four critical unmet needs:

1. Improvement in Post-Prandial Glucose Control

Given intra-patient variability and day-to-day changes in activity and food consumption, basal (long-acting) insulins are often insufficient in achieving HbA1c levels [1], [2]. Although exact estimates vary, only 21.0% of patients with type 1 diabetes (T1D) and 38.9% of patients with type 2 diabetes (T2D) utilizing basal insulins achieve HbA1c goals [3], [4]. A large, real-world retrospective analysis of almost 40,000 patients with T2D on basal insulin in the US found that 73% of patients did not meet HbA1c goals, and that rapid-acting insulin was added for 32.6% of patients overall, including 43% of ongoing users of basal insulin [5]. This pattern was also seen for patients who did not achieve fasting blood glucose goals on basal insulin alone; 27.3% of those patients added a rapid-acting insulin [5].

HbA1c levels are determined by both fasting plasma glucose (FPG) and post-prandial plasma glucose (PPG) levels, and therefore effective management of both components is essential [6]. Many patients have acceptable FPG levels yet fail to achieve the recommended HbA1c target <7%. Studies have demonstrated that PPG contributes significantly to overall HbA1c levels, with a greater relative effect (up to 70%) observed when patients are nearing HbA1c levels of 7% [7]. However, post-prandial hyperglycemia or elevated PPG level after meals is still common in patients with diabetes [8]. Rapid-acting insulin analogs like NovoLog® and ultra-rapid acting insulin analogs like FIASP® closely match the physiological insulin profile of a person without diabetes when compared with regular human insulin to ensure better glycemic control [9].

Prandial insulins address a key unmet need in diabetes care by providing better glucose control to avoid adverse effects of high blood glucose following meals. Additionally, without prandial insulins, patients face the risk of over-basalization, or being prescribed excessive basal insulin doses to achieve glycemic targets, which ultimately results in a proportionally higher risk of hypoglycemia and weight gain [10], [11]. Therefore, rapid-acting and ultra-rapid acting insulins address a key unmet need of treatment intensification, particularly around meals, for patients living with T1D and T2D.

2. Avoidance of Long-term Complications

Complications due to poor glycemic control is a key contributor to the burden of diabetes. In the Diabetes Control and Complications Trial (DCCT), compared to patients on intensive therapy (aimed at achieving levels of glycemia as close to the nondiabetic range as safely possible), patients on conventional therapy (relatively poor glycemic control), had a higher incidence of retinopathy, nephropathy, and cardiovascular complications [12]. Furthermore, the presence of complications is associated with a significant increase in the likelihood of having depression or anxiety [13]. Complications due to poor glycemic control is a significant contributor to the cost of care in diabetes and is estimated to account for 53% of all diabetes-related costs [14]. There is always a need for newer and improved products that effectively keep blood sugar levels under control and prevent long term complications in T1D and T2D.

3. Overcoming Restrictions on Daily Activities and Challenging Mealtime Dosing Requirements

Although American Diabetes Association (ADA) guidelines recommend that rapid-acting insulin analogs be injected before meals as indicated (EISayed), evidence suggests that many patients do not follow recommendations and dose insulin after their meal (Peters), [17], [18]. This can result in poor post-prandial glucose control which can lead to short and long-term complications. An analysis of data from the T1D Exchange registry involving 21,533 patients revealed that 32% of patients dosed insulin after their meal (Peters). An independent, online survey of adults with T1D, and parents and physicians of children with T1D found that 91% of adults and 97% of parents experienced at least one major challenge with mealtime insulin dosing (Lane). Reported challenges that occurred at least once a week included eating more or less food than anticipated after dosing mealtime insulin (70% of adults and 81% of parents of children); needing to eat additional food as a corrective action to prevent hypoglycemia as a result of eating a meal that had less carbohydrates than anticipated (58% of adults and 70% of parents of children); and needing to administer additional corrective insulin after consuming more food than was anticipated (57% of adults and 65% of parents of children) (Lane). FIASP®'s improved time-action profile, more rapid onset of action, and demonstrated efficacy can help alleviate the need for corrective actions after meals by allowing for more flexible insulin dosing around meals while mitigating concerns about PPG excursions (Lane).

4. Novel Delivery Systems That Respond to Evolving Patient Needs

Advancements in modern insulin development including rapid-acting and ultra-rapid analogs have spurred progress in insulin delivery devices and glucose monitoring technology (Kurtzhals). One of these advancements is insulin pumps which generally use rapid-acting insulin formulations and are mainly used by individuals living with T1D, although 10% of pump users live with T2D [21]. The use of insulin pumps has increased dramatically in the United States from <7,000 users in 1990 to nearly 100,000 in 2000 and >350,000 in 2022 [22]. Advantages of insulin pumps include precise dosing, flexibility (continuous insulin delivery and programmability to adjust dose), and convenience (push-of-a-button insulin delivery) compared to vials and syringes. Insulin pens

represent another technological advance which are more convenient, less painful, easily storable and transportable, have greater ease of use, and greater social acceptability compared to vials/syringes [23], [24].

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Q32: Executive Summary

For 100 years, Novo Nordisk Inc. has been committed to driving change to improve treatment for individuals living with type 1 diabetes (T1D) and type 2 diabetes (T2D), from more effective medicines to better delivery systems that make management simpler, more convenient, and reduce the burden of living with a chronic disease. As part of its expansive diabetes R&D program, Novo Nordisk Inc. has made significant investments in developing rapid-acting NovoLog® (approved 7/7/2000) and ultra-rapid acting FIASP® (approved 9/28/2017).

Both NovoLog® and FIASP® are indicated to improve glycemic control in adult and pediatric patients with T1D and T2D. While their indications are the same, NovoLog® and FIASP® are two unique products which belong to different classes of prandial insulins, NovoLog® in the rapid-acting class and FIASP® in the ultra-rapid acting class. The American Diabetes Association (ADA) Guidelines states that the preferred insulin regimen for patients with T1D is a long-acting insulin with flexible doses of an ultra-rapid acting analog or a rapid-acting analog at meals. In a randomized, single-centered, double-blind, 3-period crossover study in 51 patients with T1D, it was shown that FIASP® appears in the bloodstream two times faster than NovoLog®. FIASP® also has more flexible subcutaneous administration as it can be dosed at the start of a meal or 20 minutes after starting a meal, while NovoLog® is to be dosed before or within 5-10 minutes of the start of the meal. Finally, three pivotal, treat-to-target, non-inferiority clinical trials showed that mealtime administration of FIASP® outperformed NovoLog® in terms of reducing the post-prandial glucose (PPG) control, or glucose control after a meal, at 1-hour after patients were provided the same amount of carbohydrate.

For the reasons mentioned above as well as the additional details discussed within Section I, the most “clinically comparable therapeutic alternative” to NovoLog® are other rapid-acting insulins Humalog and its follow-on biologic ADMELOG, while the most “clinically comparable therapeutic alternative” to FIASP® is another ultra-rapid insulin, Lyumjev. It is important to note that ADMELOG’s indication differs from both NovoLog®’s and Humalog’s as it is indicated to improve glycemic control in adults and pediatric patients 3 years and older with T1D and only adults with T2D. [REDACTED]

[REDACTED]

When comparing these products, it is important to consider several different factors including clinical efficacy, safety, patient experience, and how they are administered, which also plays a major role in patient experience. Starting with clinical efficacy, the outcomes that should be considered are Hemoglobin A1c (HbA1c), PPG control, and safety. As explained in the response to question 28, there is no simple and straightforward way to compare the clinical efficacy between therapeutic alternatives. First, in their pivotal trials, both NovoLog® and Humalog were compared to regular human insulin as that was the only prandial insulin available at that time. Over 15 years later, FIASP® and Lyumjev, both ultra-rapid acting insulins, were compared to rapid-acting insulins during their pivotal clinical trial programs, as these represented the standard of care. Therefore, while data from these clinical trials has been presented and summarized, no direct head-to-head clinical comparisons can be made between NovoLog® and Humalog or FIASP®

and Lyumjev. In addition to this, both clinical trial programs were designed as treat-to-target per FDA guidance, meaning that the patients enrolled had their insulin titrated to achieve a known and validated HbA1c score. While it is important to consider the impact rapid-acting and ultra-rapid acting insulins have on outcomes compared to their comparators, it is difficult given the structure of the clinical trials.

An important result from the trials was NovoLog® and FIASP®'s impact on PPG control versus their comparators. In patients with T1D, when compared with regular human insulin, NovoLog® provided significantly superior PPG control. The same can be said for FIASP® versus its comparator NovoLog®. PPG levels contribute significantly to overall HbA1c. The Diabetes Control and Complications study (DCCT) showed definitively that better glycemic control in patients with T1D is associated with a reduction in rates of development and progression of microvascular complications such as retinopathy, neuropathy, and diabetic kidney disease, while there is robust evidence linking high PPG levels with the development of vascular complications. Approximately 61% of healthcare expenditures in diabetes are attributed to elderly patients over 65 years of age, much of which is represented by vascular complications including cardiovascular-related care. Owing to their impact on PPG levels, NovoLog® and FIASP® are important treatment options that can potentially have a positive impact on complications and healthcare resource use in patients with T1D and T2D.

Rapid-acting and ultra-rapid acting insulins like NovoLog® and FIASP®, respectively, improve patient experience. An independent, online survey of adults with T1D, and parents and physicians of children with T1D found that 91% of adults and 97% of parents experienced at least one major challenge with mealtime insulin dosing. Therefore, products such as FIASP®, which can be administered at the beginning of a meal or 20 minutes after, are particularly valuable as it allows patients more flexibility when compared to products which must be dosed before a meal.

NovoLog® and FIASP® are both available in multiple modes of administration which must be considered when determining the value of each NDC. Patients using vial/syringe are at greater risk of drawing up an incorrect insulin dose, with an estimated relative error of 19%, which is a significant risk and concern for patients, especially elderly patients. An open-label randomized crossover study showed that 73% of patients felt more confident in the accuracy of the insulin dose delivered with a pen while a separate study evaluating patient satisfaction associated with the method of insulin administration found that those using pens were more likely to adhere to their insulin therapy, resulting in fewer hypoglycemic episodes and associated healthcare costs.

Public E2 Submission

IPAY: 2026



Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	INSULIN ASPART
	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	

Public E2 Submission

IPAY: 2026



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

Question 31:
Patient and
Caregiver
Experience

Response to Question 31

Response

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 take Novolog to manage the condition. When asked what would happen if she could not obtain her insulin, [REDACTED] says, "I'll die, number one." [REDACTED] feels strongly that drugmakers should lower the costs of insulin. "Considering it probably cost them all of about \$2 to make a bottle of insulin, MAYBE \$2, their markup is over 300%. It's absolutely ludicrous. I know the games. I get it, especially with the name brand products and companies. You're paying for all the R&D, but still, it doesn't come out to the astronomical cost that they [drug manufacturers] charge people." ..AARP fiercely believes that the needs of Medicare beneficiaries should remain paramount as the agency implements the Negotiation Program. In 2022, about 1 in 5 adults ages 65 and up either skipped, delayed, took less medication than was prescribed, or took someone else's medication last year because of concerns about cost. It is not fair or right to ask patients and taxpayers to continue paying for high prescription drug prices that are the result of broken markets. ..Successful implementation of the new federal law will help reduce prescription drug prices and costs and ensure that millions of older Americans are better able to access the prescription drugs they need at a price they can afford. The Medicare drug price negotiation process will also finally allow CMS to push back on indiscriminately escalating drug prices and ensure that taxpayer funds are paying for value – all while saving billions for Medicare and its beneficiaries. The CBO estimates that the Negotiation Program will save Medicare and the American taxpayers nearly \$98.5 billion over 10 years, reduce the budget deficit by \$25 billion in 2031, and save Medicare Part D enrollees \$7 billion in 2031 due to lower out-of-pocket costs and premiums. ..This is about real people whose lives are on the line. For decades, older Americans have paid the highest prices in the world for prescription drugs - often three times higher than people in other countries. Now is the time to change that. Effective implementation of this Program will represent a major victory for

Public E2 Submission

IPAY: 2026



Question Sub-Question

Response

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

Question 32:
Executive
Summary

Response to Question 32



October 2, 2023

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

Dear Dr. Seshamani:

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

Data shows that brand-name drug prices have increased dramatically faster than inflation for decades. List prices for the 25 brand-name drugs with the highest total Medicare Part D spending in 2021 have increased by an average of 226%—or more than tripled—since they first entered the market.¹ Data also shows that all but one of the top 25 drugs' lifetime price increases greatly exceeded the corresponding annual rate of general inflation (Consumer Price Index All Urban Consumers for All Items; CPI-U) over the period that each product has been on the market (i.e., product launch date until May 2023).² For example, the price of Enbrel (Etanercept), used to treat rheumatoid arthritis and psoriatic arthritis, has increased by 701% since coming to market in 1998, and the price of Januvia (Sitagliptin), used to treat diabetes, has increased by 275% since entering the market in 2006.³ Further, the median price of a new brand-name prescription drug is now approximately \$200,000 per year,⁴ so even relatively small percentage price increases can translate into thousands of dollars and put life-saving medications out of reach of the patients who need them.

High prescription drug prices can negatively affect older adults' health and financial security. ██████, a Medicare enrollee from ██████, is living with a health condition and take Novolog to manage the condition. When asked what would happen if she could not obtain her insulin, ██████ says, "I'll die, number one." ██████ feels strongly that drugmakers should lower the costs of insulin. "Considering it probably cost them all of about \$2 to make a bottle of insulin, MAYBE \$2, their markup is over 300%. It's absolutely ludicrous. I know the games. I get it,

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/>.

especially with the name brand products and companies. You're paying for all the R&D, but still, it doesn't come out to the astronomical cost that they [drug manufacturers] charge people.”

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.*

Public E2 Submission

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Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	INSULIN ASPART
	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 Aamed Alliance believes this information is crucial for appropriately determining the negotiated prices, we are concerned that relying on 20 randomly selected speakers will not provide CMS with a comprehensive perspective on these medications and their benefits to patients, providers, and caregivers. We are also concerned that this random selection process could unintentionally exclude speakers who shed light on health equity, minority health, and other access issues.¹² Therefore, we urge CMS to expand the number of listening sessions to ensure CMS appropriately considers the broad implications and health equity considerations of these treatments; and how these price negotiations could impact access for diverse communities.

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

IV. Conclusion

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

Sincerely,
Ashira Vantrees
Counsel

¹¹ *Id.*

¹² Khiara Bridges, *Implicit Bias and Racial Disparities in Health Care*, https://www.americanbar.org/groups/crsj/publications/human_rights_magazine_home/the-state-of-healthcare-in-the-united-states/racial-disparities-in-health-care/

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

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

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Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	INSULIN ASPART
	Q26 - Respondent Name	
	Q26 - Organization Name (if applicable)	American Diabetes Association
	Respondent Email	
Question 27: Prescribing Information	Who is completing this form?	PAO
	Prescribing Information	Novolog and Fiasp are distinct products. .Novolog (a rapid-acting insulin) and Fiasp (an ultra-rapid-acting insulin) are two different products. Both insulins can provide meaningful benefits to patients who use them, clinically, and in the day-to-day patient experience. Ultra-rapid acting insulin analogs are utilized to improve glycemic control in adults and .children with Type 1 and Type 2 diabetes. This drug contains the active ingredient insulin aspart, but also contains the addition of vitamin B3 (niacinamide) to increase the speed of initial absorption and an amino acid (L-arginine) to stabilize the formulation. This results in a faster-acting insulin with differentiated dosing administration for use in Type 1 and Type 2 diabetes. These ultra-rapid acting insulin analogs appear in the .bloodstream faster than a rapid acting insulin.
	Evidence Submitted include a cost-effectiveness measure?	N
Question 28: Therapeutic Impact and Comparative Effectiveness	What type of Evidence is shown?	
	Therapeutic Impact and Comparative Effectiveness	Human insulin is not a therapeutic alternative to NovoLog or FIASP...The ADA Standards of Care 2023 differentiates between short-acting and rapid acting insulin when we state that patients with Type 1 diabetes should use rapid-acting insulin analogs, as they are associated with less hypoglycemia (low-blood glucose) and weight gain, as well as lower A1C compared with short-acting human insulins. The preferred insulin regimen for patients with Type 1 diabetes is a long-acting analog with flexible doses of an ultra-rapid acting analog or a rapid-acting analog at meals. In brief, the faster onset of action of the rapid acting class reduces complications. Equating short acting human insulin with rapid acting insulin, may result in superseding the decisions of the patient and their physician who know what is best for their care.

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

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Question	Sub-Question	Response
Medical Needs	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	<p>October 2, 2023..The Honorable Chiquita Brooks-LaSure .Administrator.Centers for Medicare & Medicaid Services,.Department of Health and Human Services .Baltimore, MD 21244-8016 ..Dear Administrator Brooks-LaSure, ..The American Diabetes Association (ADA) is pleased to submit comments to the Centers for Medicare & Medicaid Services (CMS) regarding the Medicare Drug Price Negotiation Program. We appreciate the steps that the agency has taken in recent years to make medications more affordable for seniors. With four of the ten drugs selected for the first round of negotiation used to treat diabetes, the ADA takes a considerable .interest in this process to ensure that individuals with diabetes feel the impacts of these potentially lower cost medications. ..As you are aware, the cost of health care is one of the most consequential issues for the diabetes community today – and is among the greatest barriers to the health and well-being for Americans living with this illness. To date, health care costs for Americans with diabetes are 2.5 times higher than for those without diabetes. ADA is the leading voice advocating for insulin affordability; and has worked to enact legislation in twenty-five states and the District of Columbia. The ADA remains equally focused on both lowering the cost of drugs at the pharmacy counter, as it is the systemic costs, more broadly. ..About ADA.The ADA is a nationwide, nonprofit, voluntary health organization founded in 1940 and made up of persons with diabetes, healthcare professionals who treat persons with diabetes, research scientists, and other concerned individuals. The ADA's mission is to prevent and cure diabetes and to improve the lives of all people affected by diabetes. The ADA, the largest non-governmental organization that deals with the treatment and impact of diabetes, represents the 133 million individuals living with diabetes and .prediabetes. The ADA also reviews and authors the most authoritative and widely followed clinical practice recommendations, guidelines, and</p>

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Question Sub-Question

Response

standards for the treatment of diabetes and publishes the most influential professional journals concerning diabetes research and treatment...Comments.We share with you below a summary of key issues that we consider most important to the interests of people living with diabetes. The ADA looks forward to working with the agency on drug pricing issues as it moves forward with the implementation of the drug negotiation program...Human insulin is not a therapeutic alternative to NovoLog or FIASP. .The ADA Standards of Care 2023 differentiates between short-acting and rapid acting insulin when we state that patients with Type 1 diabetes should use rapid-acting insulin analogs, as they are associated with less hypoglycemia (low-blood glucose) and weight gain, as well as lower A1C compared with short-acting human insulins. The preferred insulin regimen for patients with Type 1 diabetes is a long-acting analog with flexible doses of an ultra-rapid acting analog or a rapid-acting analog at meals. In brief, the faster onset of action of the rapid acting class reduces complications. Equating short acting human insulin with rapid acting insulin, may result in superseding the decisions of the patient and their physician who know what is best for their care...Novolog and Fiasp are distinct products. .Novolog (a rapid-acting insulin) and Fiasp (an ultra-rapid-acting insulin) are two different products. Both insulins can provide meaningful benefits to patients who use them, clinically, and in the day-to-day patient experience. Ultra-rapid acting insulin analogs are utilized to improve glycemic control in adults and .children with Type 1 and Type 2 diabetes. This drug contains the active ingredient insulin aspart, but also contains the addition of vitamin B3 (niacinamide) to increase the speed of initial absorption and an amino acid (L-arginine) to stabilize the formulation. This results in a faster-acting insulin with differentiated dosing administration for use in Type 1 and Type 2 diabetes. These ultra-rapid acting insulin analogs appear in the .bloodstream faster than a rapid acting insulin. ..Conclusion.The American Diabetes Association appreciates the opportunity to submit these comments on the Medicare Drug Price Negotiation Program. On behalf of the community of 133 million Americans with diabetes and prediabetes, we appreciate the attention that CMS is paying to this issue. We would welcome the opportunity to provide further assistance as the agency formulates additional pricing and payment policies. .Should you have any questions or seek additional information regarding these comments, please reach out to Laura Friedman, Vice President, Regulatory Affairs at: lfriedman@diabetes.org...Sincerely, ..Robert A. Gabbay, M.D., PhD.Chief Scientific and Medical Officer

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Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	INSULIN ASPART
	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 restrictions to access or utilization management, is also important to patients.
	Evidence Submitted include a cost-effectiveness measure?	N
Question 28: Therapeutic Impact and Comparative Effectiveness	What type of Evidence is shown?	
	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 aggregated data. Because of this, as CMS considers how this area factors into the overall price negotiation, CMS should ensure a negotiated price reflects the value the product provides to each unique patient. CCPA believes it is important that the incentives to continue developing treatments for chronic diseases be preserved, and it is important to reward the value treatments bring to patients.

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

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Question	Sub-Question	Response
	What type of Evidence is shown?	
	Response to Question 30	The Chronic Care Policy Alliance (CCPA) is a network of advocates focused on issues affecting patients living with chronic conditions. While we will let other disease-specific organizations offer their detailed perspectives on this drug, CCPA wishes to convey its views on how CMS should use the information gathered from the public...CMS should ensure that its negotiation process on this product does not disadvantage any patient with an unmet medical need. Specifically, CMS should guard against the results of negotiations undercutting research into the product that may meet other unmet medical needs or may negatively impact the development of other products focused on unmet medical needs.
Question 30: Addressing Unmet Medical Needs	Hyperlink to Citation - Additional Materials for Question 30 Hyperlink to Table/Charts/Graphs - Additional Materials for Question 30 Evidence Submitted include a cost-effectiveness measure? 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	INSULIN ASPART
	Q26 - Respondent Name	
	Q26 - Organization Name (if applicable)	Diabetes Advocacy Alliance
	Respondent Email	
Question 27: Prescribing Information	Who is completing this form?	OTH
	Prescribing Information	See our letter.
	Evidence Submitted include a cost-effectiveness measure?	D
Question 28: Therapeutic Impact and Comparative Effectiveness	What type of Evidence is shown?	
	Therapeutic Impact and Comparative Effectiveness	See our letter.
	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	<p>October 2, 2023 ..The Honorable Chiquita Brooks-LaSure .Administrator.Centers for Medicare & Medicaid Services,.Department of Health and Human Services .Baltimore, MD 21244-8016 ..Dear Administrator Brooks-LaSure:..On behalf of the undersigned member organizations of the Diabetes Advocacy Alliance (DAA), we are pleased to submit comments to the Centers for Medicare & Medicaid Services (CMS) regarding the Medicare Drug Price Negotiation Program. ..The DAA is diverse in scope, with our members representing patient, professional and trade associations, other non-profit organizations, and corporations, all united to change the way diabetes is viewed and treated in America. Since 2010, the DAA has worked with legislators and policymakers to increase awareness of, and action on, the diabetes epidemic...DAA members share a common goal of elevating diabetes on the national agenda so we may ultimately defeat this treatable, but deadly chronic disease. We are committed to advancing person-centered policies, practical models, and legislation that can improve the health and well-being of people with diabetes and prediabetes. As such, the undersigned members have some thoughts to share with you as you proceed with the implementation of the Medicare Drug Price Negotiation Program...Make Sure to Consider Diabetes Patients Lived Experiences and Preserve Provider Ability to Choose Medications Most Appropriate for Their Individual Patients. ..While we agree that patients deserve access to affordable medications, we trust that CMS will listen to and act upon the lived experiences of people with diabetes and their health care providers. These individuals can share information on the often-dramatic benefits they have seen from the four diabetes drugs that are among the first 10 medications that CMS has selected for price negotiations and can attest to negative health impacts that can accompany switching patients to medications that CMS considers therapeutic alternatives. ..Different individuals with diabetes may respond well to one medication in a class of drugs but not to another that CMS may consider as equivalent. Clinical guidelines from the American Diabetes Association recommend patient-centric models of care in considering treatment plans. .For example, many people with diabetes cannot switch from an insulin analog product to human insulin without experiencing deleterious effects, or from a new class of oral diabetes medications to what CMS may consider therapeutic alternatives. Equivalence in terms of clinical effects for an individual patient is not guaranteed. ..The undersigned members of the DAA also believe it is vital to preserve provider choice in prescribing medications for their patients with diabetes, as providers must consider how an individual patient responds to a medication in terms of both clinical benefits and bothersome or deleterious side effects. If providers are forced to switch their patients to therapeutic alternatives that lessen patient compliance and subsequently worsen patient outcomes, CMS will not achieve the long-term goals of its strategic plan. Following negotiations and upon implementation, CMS needs to monitor how the negotiated medications are placed in formularies, to ensure that people with diabetes do not</p>

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Question Sub-Question

Response

have to “jump through hoops” to get the medications prescribed for them. ..Be Wary of Unintended Consequences on Continued Medical Advances and Innovation..The undersigned DAA member organizations support efforts to lower costs for people with diabetes but are concerned about unintended consequences of such efforts, which could threaten innovation. Innovation in medical products and services has helped make the experience of living with diabetes more manageable today than ever before, with clinical and lifestyle benefits that have increased patient compliance, reduced rates of diabetes health complications, and made living with this serious chronic disease less burdensome. We encourage CMS to keep these points in mind as it moves forward in its drug negotiation processes. ..Thank you for this opportunity to share our thoughts and concerns. ..Sincerely,..The undersigned members of the Diabetes Advocacy Alliance*..Black Women's Health Imperative .Noom, Inc. .Pediatric Endocrine Society*Note: Several other member organizations of the Diabetes Advocacy Alliance preferred to submit their own comments to CMS.



October 2, 2023

The Honorable Chiquita Brooks-LaSure
Administrator
Centers for Medicare & Medicaid Services,
Department of Health and Human Services
Baltimore, MD 21244-8016

Dear Administrator Brooks-LaSure:

On behalf of the undersigned member organizations of the [Diabetes Advocacy Alliance](#) (DAA), we are pleased to submit comments to the Centers for Medicare & Medicaid Services (CMS) regarding the Medicare Drug Price Negotiation Program.

The DAA is diverse in scope, with our members representing patient, professional and trade associations, other non-profit organizations, and corporations, all united to change the way diabetes is viewed and treated in America. Since 2010, the DAA has worked with legislators and policymakers to increase awareness of, and action on, the diabetes epidemic.

DAA members share a common goal of elevating diabetes on the national agenda so we may ultimately defeat this treatable, but deadly chronic disease. We are committed to advancing person-centered policies, practical models, and legislation that can improve the health and well-being of people with diabetes and prediabetes. As such, the undersigned members have some thoughts to share with you as you proceed with the implementation of the Medicare Drug Price Negotiation Program.

Make Sure to Consider Diabetes Patients Lived Experiences and Preserve Provider Ability to Choose Medications Most Appropriate for Their Individual Patients.

While we agree that patients deserve access to affordable medications, we trust that CMS will listen to and act upon the lived experiences of people with diabetes and their health care providers. These individuals can share information on the often-dramatic benefits they have seen from the four diabetes drugs that are among the first 10 medications that CMS has selected for price negotiations and can attest to negative health impacts that can accompany switching patients to medications that CMS considers therapeutic alternatives.

Different individuals with diabetes may respond well to one medication in a class of drugs but not to another that CMS may consider as equivalent. Clinical guidelines from the American Diabetes Association recommend patient-centric models of care in considering treatment plans.

For example, many people with diabetes cannot switch from an insulin analog product to human insulin without experiencing deleterious effects, or from a new class of oral diabetes medications to what CMS may consider therapeutic alternatives. Equivalence in terms of clinical effects for an individual patient is not guaranteed.

The undersigned members of the DAA also believe it is vital to preserve provider choice in prescribing medications for their patients with diabetes, as providers must consider how an individual patient responds to a medication in terms of both clinical benefits and bothersome or deleterious side effects. If providers are forced to switch their patients to therapeutic alternatives that lessen patient compliance and subsequently worsen patient outcomes, CMS will not achieve the long-term goals of its strategic plan. Following negotiations and upon implementation, CMS needs to monitor how the negotiated medications are placed in formularies, to ensure that people with diabetes do not have to “jump through hoops” to get the medications prescribed for them.

Be Wary of Unintended Consequences on Continued Medical Advances and Innovation

The undersigned DAA member organizations support efforts to lower costs for people with diabetes but are concerned about unintended consequences of such efforts, which could threaten innovation. Innovation in medical products and services has helped make the experience of living with diabetes more manageable today than ever before, with clinical and lifestyle benefits that have increased patient compliance, reduced rates of diabetes health complications, and made living with this serious chronic disease less burdensome. We encourage CMS to keep these points in mind as it moves forward in its drug negotiation processes.

Thank you for this opportunity to share our thoughts and concerns.

Sincerely,

The undersigned members of the Diabetes Advocacy Alliance*

Black Women’s Health Imperative

Noom, Inc.

Pediatric Endocrine Society

*Note: Several other member organizations of the [Diabetes Advocacy Alliance](#) preferred to submit their own comments to CMS.

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Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	INSULIN ASPART
	Q26 - Respondent Name	
	Q26 - Organization Name (if applicable)	Diabetes Leadership Council
	Respondent Email	
Question 27: Prescribing Information	Who is completing this form?	PAO
	Prescribing Information	
	Evidence Submitted include a cost-effectiveness measure?	
Question 28: Therapeutic Impact and Comparative Effectiveness	What type of Evidence is shown?	
	Therapeutic Impact and Comparative Effectiveness	
	Hyperlink to Table/Charts/Graphs - Additional Materials for Question 28	
	Evidence Submitted include a cost-effectiveness measure?	N
Question 29: Comparative Effectiveness	What type of Evidence is shown?	
	Response to Question 29	On behalf of the Diabetes Leadership Council (DLC), thank you for the opportunity to provide patient-focused comments on four diabetes therapies included in the first 10 Medicare Part D drugs that the Centers for Medicare & Medicaid Services (CMS) selected for price negotiation. ..DLC unites former leaders of national

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Question	Sub-Question	Response
on Specific Populations		<p>diabetes organizations who are dedicated to advancing patients-first policies. We are people with diabetes, parents of children with diabetes, allies and tireless volunteers dedicated to improving the lives of all people impacted by this condition. ..As advocates, we see first-hand how the diabetes community fares under an opaque and complex system that requires sick people to subsidize the healthy. Patients with chronic conditions like diabetes get stuck paying inflated costs for essential medicines under the false premise that it keeps costs lower for everyone else. People with diabetes shouldn't have to shoulder the burden for policymakers' failure to fix the dysfunctional drug pricing system. We write to urge CMS to consider the impact that its decisions will have on actual patients, and to underscore that price negotiations alone will not ensure affordable, equitable prescription drug access for Medicare beneficiaries. ..HIGH COST, HIGH UTILIZATION.Diabetes has a large and growing patient population and ranks among the top three therapy classes in terms of utilization and drug spend for both commercial insurance and Medicare. As evidenced by their overrepresentation on the initial list of drugs subject to price negotiation, diabetes therapies contribute to CMS costs not only due to price, but high volumes dispensed. The fact that four of the first ten therapies subject to negotiation are diabetes treatments also highlights the heavy toll of under-resourced and under-utilized prevention efforts in the face of the diabetes epidemic. Nearly one-third of Medicare beneficiaries have diabetes and another 26.4 million people aged 65 years or older (48.8%) have prediabetes. CMS must ensure that its efforts produce tangible improvements in prescription drug access and affordability for beneficiaries managing diabetes today and in the future. ..ACCESS TO CARE.Diabetes is a highly competitive and heavily contracted category where discounts and rebates reduce net prices to levels much lower than gross or list prices. Diabetes medications already represent 42% of the \$48.6 billion in prescription drug rebates and discounts paid annually by Part D in the US. ..Beneficiary use of highly rebated or discounted drugs has different implications for plan sponsors, Medicare and patients. It can mean lower Medicare drug spending, as its plan sponsor payments are based on net drug costs after rebates. Individual beneficiary drug payments, however, may be based on the gross cost before accounting for rebates. The General Accounting Office (GAO) recently found payments by beneficiaries exceeded plan sponsor payments, after accounting for rebates, for 79 of the 100 drugs receiving the most rebate. Three therapeutic drug classes accounted for 73% of rebates: (1) endocrine metabolic agents, including antidiabetic drugs; (2) blood modifiers, including anti-stroke drugs; and (3) respiratory agents, including anti-asthma drugs. The same GAO report found instances where plan sponsors preferred rebated brand-name drugs with higher beneficiary costs over lower-cost alternatives. ..DIRECT PATIENT BENEFIT.Patients should directly benefit from drug prices negotiated on their behalf, whether negotiations are conducted by a government agency or commercial entity...CMS's price negotiations may be successful in extracting price concessions from manufacturers. Unfortunately, the program lacks any requirement to improve affordability and access for the very patients whose lives depend on these products. Instead, the program perpetuates the existing inequities that leave patients paying more for less while intermediaries pocket the savings. Patients who rely on the diabetes medications selected for price negotiations should see all rebates or discounts reflected in the price they pay at the pharmacy counter. ..Additionally, products subject to negotiated prices</p>

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Question	Sub-Question	Response
		<p>should be immediately added to Medicare formularies at the lowest cost-sharing tier and without utilization management or other barriers to appropriate use. Part D plans should encourage use of lower cost, therapeutically appropriate products by eliminating prior authorization, step therapy and other access barriers. ..ADDITIONAL CLARIFICATION NEEDED. We appreciate CMS's continued commitment to reduce insulin costs; however, we urge the agency to exercise caution and provide additional clarity for patients, providers and payers regarding insulin aspart. First, the agency has combined different insulin products with a shared active ingredient into a single entry in the initial list of products subject to negotiations. These insulin products are not interchangeable, as CMS will no doubt hear in its patient-focused listening sessions and read in comments submitted by advocates and providers. They have different real-world uses and separate FDA approvals. We ask CMS to protect beneficiary access and ensure that Part D plans do not inappropriately exclude an insulin product from coverage because the plan covers a non-interchangeable product with the same active ingredient...Second, it is unclear how negotiated prices for insulin products will interact with Inflation Reduction Act provisions that require Medicare plans to cap patient costs for at least one insulin per type and form. The diabetes community welcomed this landmark improvement in insulin affordability for Medicare beneficiaries. We want to ensure that implementation of the Medicare Price Negotiation Program furthers these access and affordability gains, rather than putting them at risk. ..Thank you for your consideration.</p>
	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?	
	Response to Question 30	

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Question	Sub-Question	Response
Question 30: Addressing Unmet Medical Needs	Hyperlink to Citation - Additional Materials for Question 30 Hyperlink to Table/Charts/Graphs - Additional Materials for Question 30 Evidence Submitted include a cost-effectiveness measure? 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>On behalf of the Diabetes Leadership Council (DLC), thank you for the opportunity to provide patient-focused comments on four diabetes therapies included in the first 10 Medicare Part D drugs that the Centers for Medicare & Medicaid Services (CMS) selected for price negotiation. ..DLC unites former leaders of national diabetes organizations who are dedicated to advancing patients-first policies. We are people with diabetes, parents of children with diabetes, allies and tireless volunteers dedicated to improving the lives of all people impacted by this condition. ..As advocates, we see first-hand how the diabetes community fares under an opaque and complex system that requires sick people to subsidize the healthy. Patients with chronic conditions like diabetes get stuck paying inflated costs for essential medicines under the false premise that it keeps costs lower for everyone else. People with diabetes shouldn't have to shoulder the burden for policymakers' failure to fix the dysfunctional drug pricing system. We write to urge CMS to consider the impact that its decisions will have on actual patients, and to underscore that price negotiations alone will not ensure affordable, equitable prescription drug access for Medicare beneficiaries. ..HIGH COST, HIGH UTILIZATION. Diabetes has a large and growing patient population and ranks among the top three therapy classes in terms of utilization and drug spend for both commercial insurance and Medicare. As evidenced by their overrepresentation on the initial list of drugs subject to price negotiation, diabetes therapies contribute to CMS costs not only due to price, but high volumes dispensed. The fact that four of the first ten therapies subject to negotiation are diabetes</p>

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Question Sub-Question

Response

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Question

Sub-Question



Response

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Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	INSULIN ASPART
	Q26 - Respondent Name	
	Q26 - Organization Name (if applicable)	Idaho #insulin4all Chapter, State Working Group of T1International
	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 was diagnosed with type 1 diabetes at a time when only human insulin was available. When analog insulins like Novolog came out, they made life easier, giving me better control of my diabetes. I've taken Novolog on and off throughout the last 30 years (on and off because I've never been able to choose which insulin to use - insurance always dictate this, so sometimes it has been Novolog and sometimes it has been Humalog)...There are definitely challenges accessing or taking this drug. Having been diagnosed with diabetes in my teens, I have never experienced adult life without the ever-present worry of if I can afford to continue to stay alive in a very real biological sense due to being able to access insulin and related supplies. I have always had to have insurance to help assuage some of the costs, even though it's also very expensive, and doesn't come with any guarantees that insulin, or a particular type of insulin like Novolog, will be covered. This has kept me from pursuing some job opportunities, no matter what they might offer to my professional path, because they didn't offer healthcare. ..And, before the ACA went into effect, access to insulins like Novolog was even harder. I would be automatically disqualified from regular health insurance and have to apply to an even more expensive health insurance "pool" for myself and the other "rejects." It took more work to apply, and was a more expensive monthly premium, with higher deductible and covered less. ..Even with insurance, however, regardless of whether I had insurance before or after the ACA, I have never been able to choose my insulin, or use exactly what my doctor would prefer – it has always been dictated to me by insurance formularies. These formularies not only dictate what I've been able to use, whether that is Novolog or not, sometimes they change mid-year, causing me to have to make an appointment with my doctor, pay the fee for that appointment, acquire a new prescription for the covered insulin, and get a new refill. When I've been in between jobs due to moving or taking a new position, I have had the *horrible* task of deciding what to do when it comes to insurance and hence access to medications like insulin. Do I risk going without insurance for a bit? Or do I pay exorbitantly costly (usually triple or more of one's regular premium) with COBRA (if I can even afford those)? And, because our healthcare is tied to employment in the US, there is ALWAYS the risk of losing access to insulin due to no fault of our own. If an employer downsizes and you are laid off and lose your benefits, you lose your access to insulin, unless you have the hundreds/thousands of dollars to buy it out of pocket each month.</p>
Question 32: Executive Summary	Response to Question 32	

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Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	INSULIN ASPART
	Q26 - Respondent Name	
	Q26 - Organization Name (if applicable)	T1International USA
	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 was diagnosed with type 1 diabetes as a senior in college in 2012 and was immediately put on insulin pens. Having this access to easier-to-use insulin was critical for me to be able to go home and back to school and back on the crew team where I was the captain of the varsity team. While learning how to count carbs and deal with my new diagnosis was a significant adjustment, being able to have insulin pens made this transition a bit smoother for me. The first time I picked up my insulin pens from the pharmacy, I remember being nervous about if I was going to be able to afford them - I had heard about the high price of insulin before being diagnosed. .While my college insurance covered a significant portion of my insulin costs, leaving me with a reasonable copay, my diabetes diagnosis did change my financial future in other ways. I was hoping to pursue what I had studied: international drinking water and sanitation. However, the jobs that I had applied for were in areas without consistent access to quality health care and didn't all provide insurance or other amenities that I needed in order to stay healthy. I ended up withdrawing my pending job applications and applying for jobs much closer to home and with really good insurance policies. I then decided to stay in jobs that were not furthering my career because I was scared to have a transition period between insurance coverages due to the high price of insulin and testing supplies..After college, I went on an insulin pump and transitioned to using insulin vials, keeping pens of long and short acting insulin on hand in case of emergencies. The short acting Novo Nordisk insulin products were exactly the same product and filled the same need for my health, but it was necessary that I have both dosage forms to stay healthy. .As a patient with diabetes, I don't get to chose what kind of insulin I use. My employer chooses the insurance company that works with the PBM and the manufacturers and wholesalers who decide what insulin they will cover for me and make me jump through onerous hoops if I dare to suggest that a different insulin works better with my body..There have been times I've had accidents, leaving insulin in a car that was too hot or too cold, or opening a box of new insulin while on a trip away from home and finding I had packed an empty box, or having a house sitter put a shipment of insulin in the freezer instead of the fridge. These moments send a shiver down my spine as they terrify me. Not only could I actually die if I couldn't get another vial of insulin in a few hours, but getting that insulin could ruin me financially. I have had to pay hundreds of dollars out of pocket (after hours on the phone dealing with moving my prescription and with my insurance) to get one vial of insulin to be able to make it home or to make it to when my insurance will kick in again. I've had to ration insulin because my credit card has been denied when I've gone to get that one vial of insulin, and I've watched my blood sugar climb as I worked to make my way home before it was too late.</p>
Question 32: Executive Summary	Response to Question 32	

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Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	INSULIN ASPART
	Q26 - Respondent Name	
	Q26 - Organization Name (if applicable)	T1International
	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

Question 31:
Patient and
Caregiver
Experience

Response to Question 31

Response

I was diagnosed with type 1 diabetes when I was 4 years old in 2003. My grandmother was taking care of me and noticed that I was taking frequent trips to the bathroom and did not feel well. She made an appointment for the pediatrician the next morning and when we went they tested my blood sugar which read over 600 and advised that she take me to the emergency room immediately. The first insulin I was prescribed was Eli Lilly's Humalog and after two years of taking that, my doctor decided I should use Novolog for better control. This switch allowed me to be a healthy child again because I was not nearly as restricted as I was on Humalog and my body reacted better to Novolog in general. I had less lows, it did not burn when it was injected, and due to the efficiency of the insulin I was able to adjust my insulin to carb ratios and correction factors so I used less units and was able to prolong the amount of time it took to go through a bottle. I used Novolog pens for a period of time as well which was very convenient and they were much easier to travel with instead of worrying about the vials being cold or being dropped and breaking. Novolog was especially helpful when I started pump therapy as that has allowed me to live a life with much more freedom and less reliance on stark routine and in general, I opt to use Novolog pens on sick days and when I take a break from my insulin pump...Due to my childhood circumstance of having a single mother with no college degree and frequent job changes and losses, I received Medicaid benefits for my entire childhood and for a few years of adulthood. If it weren't for receiving my insulin free of charge thanks to those health benefits, my name could have been on the list of those lost to rationing. I also qualified for Medicaid benefits throughout college and it wasn't until I began working my first full-time job that I had to pay for my insulin. When the pandemic hit in 2020 I had trouble accessing my insulin because my endocrinologist left the office and there was only 1 doctor for the entire county where I lived. I remember walking into the office since I could not get ahold of anyone over the phone and breaking down in tears begging someone to help me get my prescription. I was scared that I could run out of insulin and due to the isolation, no one would know I wasn't okay. Thankfully, I was able to get the help I needed, but to this day I carry that anxiety. ..When I was living in [REDACTED] after starting my full time job, a 90 day supply cost me \$120. Luckily, I was living with relatives and not paying for rent or utilities because between my insulin and other diabetes supplies, the costs were outrageous. I was able to access my insulin with no issue. I moved to [REDACTED] in early 2023 and the cost of Novolog here for the same 90 day supply is only \$15 due to my \$0 deductible plan. If it weren't for my insurance, I don't know what I would do to afford my insulin and other supplies that are essential to my life. ..We need federal insulin price caps and regulations because diabetes is a huge source of stress on its own. It is a full time job that requires 24/7/365 attention with no time off. Ever. I am terrified that some day I could be in a position where I can't afford insulin and that I could lose my life due to pharmaceutical greed over something that takes so little money to produce. I hope that my future children don't ever have to endure this condition, and if they are diagnosed, then they won't have to worry about accessing and affording the liquid that keeps them alive.

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

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Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	INSULIN ASPART
	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 was diagnosed with type 1 diabetes in 2001 at the age of 10. At the time, human insulin was the insulin most widely available and prescribed, as Novolog had only been approved less than a year and wasn't yet covered by my insurance. For the first several years of my life as a patient I took human insulins (Regular & NPH). During that time I had to have a really strict scheduling for eating, both in terms of what times I could or had to eat and what I could eat. This had a huge impact on my schedule at school and when Novolog became more widely available & I was able to access it, I was so relieved because it empowered me to be able to live a more 'normal' life. Ever since, I have lived with the fear that my insurance would change and force me to return to using human insulins, reducing my ability to have the best control of my diabetes possible and live a full life. ..Between the time I was diagnosed (2001) and then time I rolled off my parents insurance (when I got married at 24), insulin pricing grew from relatively affordable to extremely cost prohibitive, especially for someone in their early 20's and early on in their career with minimal benefits. I often found myself stuck in a job that I hated in order to keep insurance because insulin and my other supplies were just too expensive without it and could have put me in a life threatening situation. I struggled to afford insulin at many points even with insurance and have had to rely on credit cards at different points in my life to ensure I could access life saving medication. Even now in my 30's, while I have great insurance, I still fear what would happen if I lost my job or my benefits changed.</p>
Question 32: Executive Summary	Response to Question 32	

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Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	INSULIN ASPART
	Q26 - Respondent Name	
	Q26 - Organization Name (if applicable)	T1 International
	Respondent Email Who is completing this form?	PAT
Question 27: Prescribing Information	Prescribing Information	<p>Insulin aspart is used as a rapid acting insulin to control blood glucose levels in individuals with Type 1 and Type 2 Diabetes. FDA approved prescribing information includes: using insulin aspart at the start of a meal or within 20 minutes after starting a meal, subcutaneously into the abdomen, upper arm, or thigh, rotating injection sites within the same region from one injection to the next to reduce the risk of lipodystrophy and localized cutaneous amyloidosis, not injecting into areas of .lipodystrophy or localized cutaneous amyloidosis. It is recommended that for subcutaneous injection that insulin aspart should generally be used in regimens with .intermediate or long-acting insulin; patients on basal-bolus treatment who forget a mealtime dose to monitor their blood glucose level to decide if an insulin dose is needed, and to resume their usual dosing schedule at the next meal. Insulin aspart is considered a long term and often lifelong treatment for management of Type 1 or 2 Diabetes. For use of insulin aspart in an insulin pump, patients are to be instructed to rotate pump sites, utilize back up subcutaneous injection in the event of pump failure, and to use insulin aspart in accordance with pump guidelines. Off-label treatments include mild-to-moderate, uncomplicated diabetic ketoacidosis, gestational diabetes mellitus, hyperglycemia in hospitalized patients.</p>
	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	<p>Key primary outcomes of insulin aspart are management of blood glucose control as part of an insulin pump or subcutaneous injection regimen (with long term acting or intermediate insulin, oftentimes) to lower A1C. Aspart represents a therapeutic advance as a rapid acting insulin as opposed to human type insulin or slower acting insulins with longer acting times that increase risk for post use hypoglycemia and make mealtime management of blood glucose more difficult. Insulin aspart is broadly used Risks of insulin aspart can include hypoglycemia, weight gain, lumps, skin rash, nose and throat inflammation, swelling in hands and feet, and low</p>

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Question	Sub-Question	Response
	<p data-bbox="262 365 609 609">Hyperlink to Table/Charts/Graphs - Additional Materials for Question 28 Evidence Submitted include a cost-effectiveness measure?</p> <p data-bbox="262 649 609 714">What type of Evidence is shown?</p>	<p data-bbox="609 251 1969 357">potassium. Insulin aspart costs \$162-312 per 10 mL. Fiasp insulin retails \$550 for a month supply, or approx. \$314 per 10 mL. Standard dosages typically include 1-2 vials of 20 mL insulin each for short acting insulin, and 1-2 vials of long acting insulin at 10 mL per month.</p> <p data-bbox="609 576 651 609">D</p>
<p data-bbox="63 998 262 1169">Question 29: Comparative Effectiveness on Specific Populations</p>	<p data-bbox="262 950 609 982">Response to Question 29</p> <p data-bbox="262 1242 609 1347">Hyperlink to Citation - Additional Materials for Question 29</p>	<p data-bbox="609 755 1969 1177">Insulin aspart is a typical part of treatment for Type 1 Diabetes to reduce blood control levels. It can be used with Type 2 Diabetes also, and in instances can be used to treat diabetic ketoacidosis, although this is not currently FDA approved. Given the limited access to therapeutic alternatives, and the life threatening ramifications of not having access to insulin aspart, access to insulin aspart should be considered a priority. Lack of glucose control can lead to serious health implications that include renal failure, diabetic retinopathy, neuropathy and falls, amputations, and poor circulation. Poor glucose control can lead to diabetic coma and death. Potential differences in the safety profile of insulin for the elderly may be considered in terms of impaired cognition that could impact safe adherence to recommended dosages. Humalog has not been studied in children under 3 years old, compared to Novolog insulin. Novolog can be used by adults and children who are at least 2 years old and who have type 1 or type 2 diabetes. Novolog takes action in the body more quickly than Humalog, so you can take it closer to a meal. The best results are achieved if you take Novolog 5 to 10 minutes before eating.</p>

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Question	Sub-Question	Response
	Hyperlink to Table/Charts/Graphs - Additional Materials for Question 29	
	Evidence Submitted include a cost-effectiveness measure?	D
	What type of Evidence is shown?	
	Response to Question 30	The price of insulin aspart has led to drug rationing and inability for patients to comply with recommended dosages from medical providers. Few therapeutic alternatives exist to meet the life threatening implications of Diabetes Mellitus. Insulin aspart products allow individuals with Diabetes an improved quality life over human insulin alternatives, with shorter acting times that allow for a more normalized eating schedule and quicker response times to correcting blood glucose levels.
	Hyperlink to Citation - Additional Materials for Question 30	https://www.goodrx.com/fiasp https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/208751s010s011lbl.pdf
Question 30: Addressing Unmet Medical Needs	Hyperlink to Table/Charts/Graphs - Additional Materials for Question 30	
	Evidence Submitted include a cost-effectiveness measure?	D
	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 have been taking the selected drug for 12 years. Proper adherence to the dosages specified by my healthcare provider has allowed me improved control of my blood glucose. The side effects are, namely, hypoglycemia. Some occasional lumps can occur with insulin injections, both via pump or via syringe or pen methods. My quality of life with insulin aspart allows me greater access to foods I may not be able to eat with other types of slower acting insulin, as well as allows me a lower A1C than other slow acting insulins. Fiasp would be my desired choice of insulin as it has the quickest acting time on the market, which would allow greater control of my blood glucose, but it is too expensive even with insurance for me to afford. Therefore, I use humalog/novolog as a short acting insulin. I have had immense challenges with affording this drug throughout my life with Diabetes - as an uninsured individual, unable to afford the price at the pharmacy, as well as with two high deductible plans, both with charged me full price for insulin. Even with better insurance coverage, the lack of generic alternatives has meant I often pay a 50% cost of the drug, which can be exorbitant, depending on the cost of the drug.</p>
Question 32: Executive Summary	Response to Question 32	

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Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	INSULIN ASPART
	Q26 - Respondent Name	
	Q26 - Organization Name (if applicable)	Michigan #Insulin4all Chapter, T1International State Working Group
	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

Question 31:
Patient and
Caregiver
Experience

Response to Question 31

Response

Diagnosis story:.I was diagnosed with Type One Diabetes in 2003. A few months prior, my sister was born and my parents had gotten a new-to-them car. A few months prior to that, we had moved into our newly built house. The diagnosis process was a nightmare. I lost a third of my body weight at barely 3-years-old and my dad said he was afraid to pick me up because I was so small. I was drinking and wetting the bed constantly, I had misbehaved so much that my mom didn't actually have anything else she could take away as a punishment, and my lips had turned blue, which delayed my diagnosis. While everyone was concerned about my tiny heart, my blood sugar crept higher and higher until I was admitted to the hospital, so sick I'd only actually move my eyes. I was in Diabetic Ketoacidosis...I stayed 3.5 days and was sent home. My parents received a bible-like Pink Panther Diabetes Education book and I only ate things that had easy-to-read nutrition labels on them. This was because I was sent home on two different insulins: NPH and Regular. NPH was the long acting insulin and Regular was intermediate. It was difficult to use, the peak times were hard to manage as a child who couldn't properly communicate how I felt, and I was on a very strict diet. My parents could feed me what they wanted, but I had to have a specific number of carbs at every meal and snack. My parents worried about giving me a bad relationship with food, so I often got juice or sugary treats with a meal to hit that carb count. Overnight, my parents would wake up about every three hours to check my blood sugar as well as whenever my newborn sister needed something. In the beginning, they had to chase me down to give me a shot...When I was diagnosed, it obviously turned my family's life upside down. The costs added up and we were unaware of a program in ██████████ called Children's Special Health. Insulin was one part of these costs, the rest of my diabetes supplies were another. Prior to the Affordable Care Act, my dad's insurance didn't have to cover my diabetes supplies or insulin at all--I had a preexisting condition. When my family was faced with the costs of all of my supplies, they made sure I got it. But it came at a huge cost. My parents sold that car they had recently gotten and found a way to keep their first car for my dad to go to work, luxuries got cut, then my mom began to eat once a day from the McDonald's dollar menu without anyone knowing so that they could save money, and my mom had considered the possibility giving my sister to my grandparents because she wasn't sure if they'd be able to raise her like this. My dad stayed at jobs with awful work environments that required him working at least 60 hours a week because we couldn't risk switching health insurances and he made too much for medicaid. To this day, my dad is limited in job opportunities because they may not cover my supplies more than the previous employer's insurance. My parents nearly got divorced so that my mom could get Medicaid for me by filing taxes as a single mother. The only reason I had and still have access to my insulin and supplies is because my parents made unthinkable sacrifices that people wouldn't know about until years later. There may be things my parents did that I still don't know about – but I will always appreciate it. All that, and that didn't even cover the day-to-day management my parents struggled with...When I was sent home from the hospital, my dad was working and my mom stayed home with me and my sister. She considered getting a job, but because I would need a 'special needs' daycare, she would essentially be working just to pay for daycare, so she continued to stay home with us. I can't imagine what other anxieties she would have had leaving me with strangers after I'd almost died. She obviously had the responsibilities that parents

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Question Sub-Question

Response

with average children have. But on top of that, she had to watch me like a hawk to figure out if my blood sugar was high or low – I was too young to know how to communicate what I was feeling. Knowing what lows and highs feel like, I can't imagine how scary it must have been knowing that my insulin with insane peak times would kick in at any time, sending me plummeting into seizure-territory. My mom also had the responsibility of making sure I get the exact right amount of insulin all day – too much could send me spiraling quickly and too much could ruin the rest of our day because I was in a bad mood – and would get up to check my blood sugar at night when my dad had to work the next day. My dad would do things too, but it wasn't the same all-day every day process while juggling a baby. But my mom did all of these things exhausted and hungry so that the rest of us could go on as normally as possible...When I was younger, there were lots of issues regarding my prescriptions. First, my insulin had to be so diluted – my tiny body and unpredictable pancreas in the 'honeymoon' phase wasn't able to handle it regularly – that it wasn't like a pharmacist could just hand us insulin off of a shelf. If my specific insulin wasn't ready, we were out of luck. Test strips for my glucose meter were like gold and I still have a good relationship with one of my pharmacists who helped my parents when it came to billing issues and insurance. She really was monumental in my upbringing because my family trusted her so much. I still ask for her if I need to talk to a pharmacist about something diabetes-related...In the mid-2000s I was the first child at my doctor's office and hospital system to be put on a flexible insulin plan consisting of a long- and rapid-acting analog insulin. It was two insulins like before, but more freedom, predictability, and less chaos. It turned my treatment from saying "at least she's not low" to "she's in range more often." As time went on, my parents would no longer have to chase me to give me a shot and my mom wouldn't have to watch me like a hawk to figure out if my blood sugar was high or low. I educated my peers at school about diabetes and what it meant, I gained more confidence in handling my disease, and most of all I didn't feel so sick. Constant cycles of high and low blood sugars are impossibly draining, and I was somewhat relieved of that. My parents were relieved at least a little bit of the terrifying peaks that NPH and Regular gave me. Things didn't magically get better, but it was a step in the right direction...Financial barriers were not the only thing that stood in the way of my diabetes treatment. When I was in second grade, I got an insulin pump. The hospital system my doctor was at in [REDACTED] wouldn't put kids my age on a pump, so we went to the [REDACTED] Children's Hospital to get it. This was about a two hour drive each way, more in the winter, and more if it was too early or too late in the day. I'd have to take an entire day off of school and it was an all-day event. My doctor (who I saw from this point all the way until I was 21 and graduated college) was amazing, and I'm sad she doesn't also do adult endocrinology. After some appointments I got set up on an insulin pump. Instead of getting a shot at every meal and my long-acting insulin once a day (which, to this day, burns so bad when I inject) I would get tiny boluses of insulin every so often and we could tailor the amount I got down to the half hour. It was life changing. Night got so much better because I was more stable. There are a lot of reasons that access to this was not only potentially life-saving for me, but also has helped ward off complications of diabetes. This pump, however, required me to go down to the [REDACTED] every three months. It was really inconvenient and would require a lot from my parents in a way that it wouldn't

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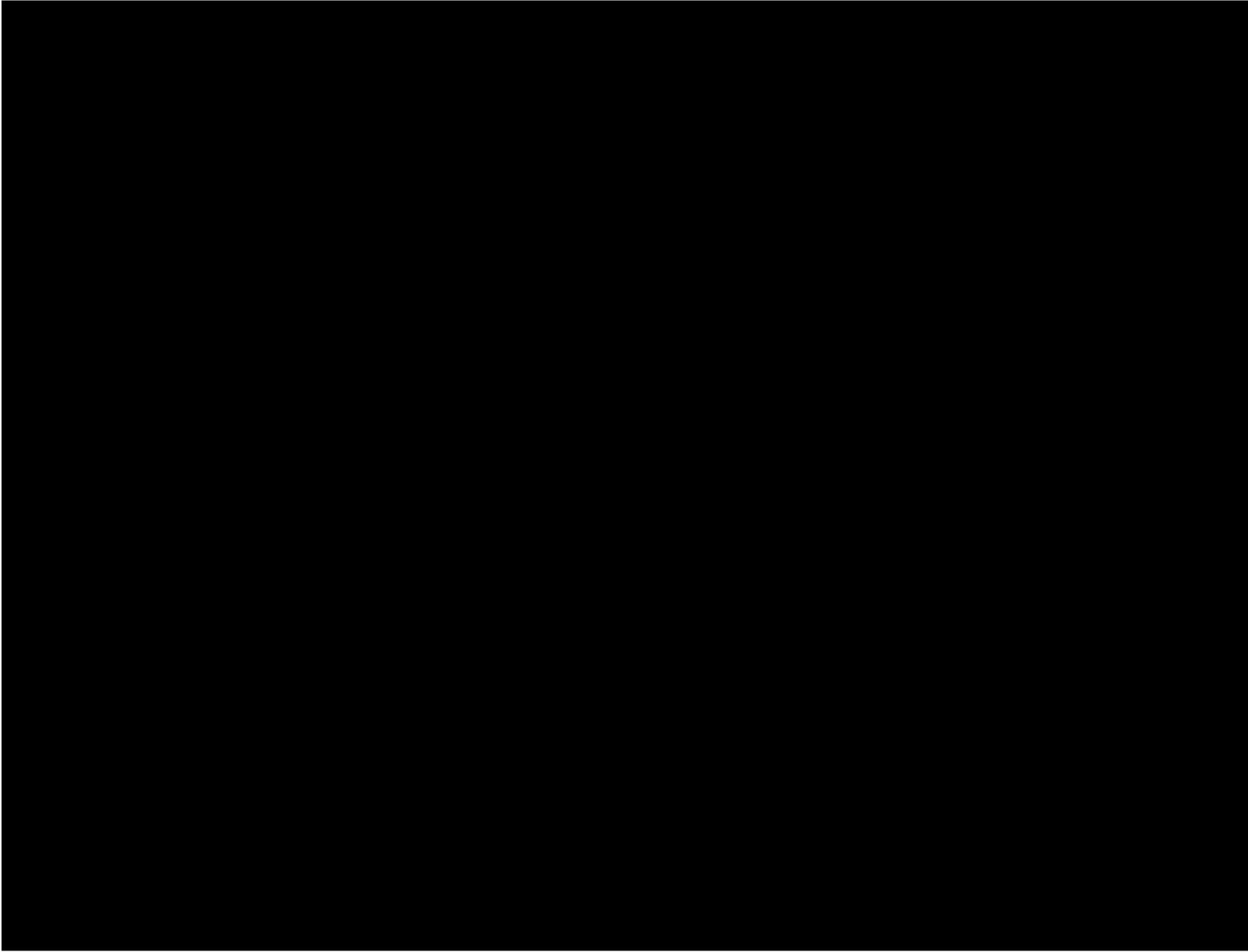
Question Sub-Question

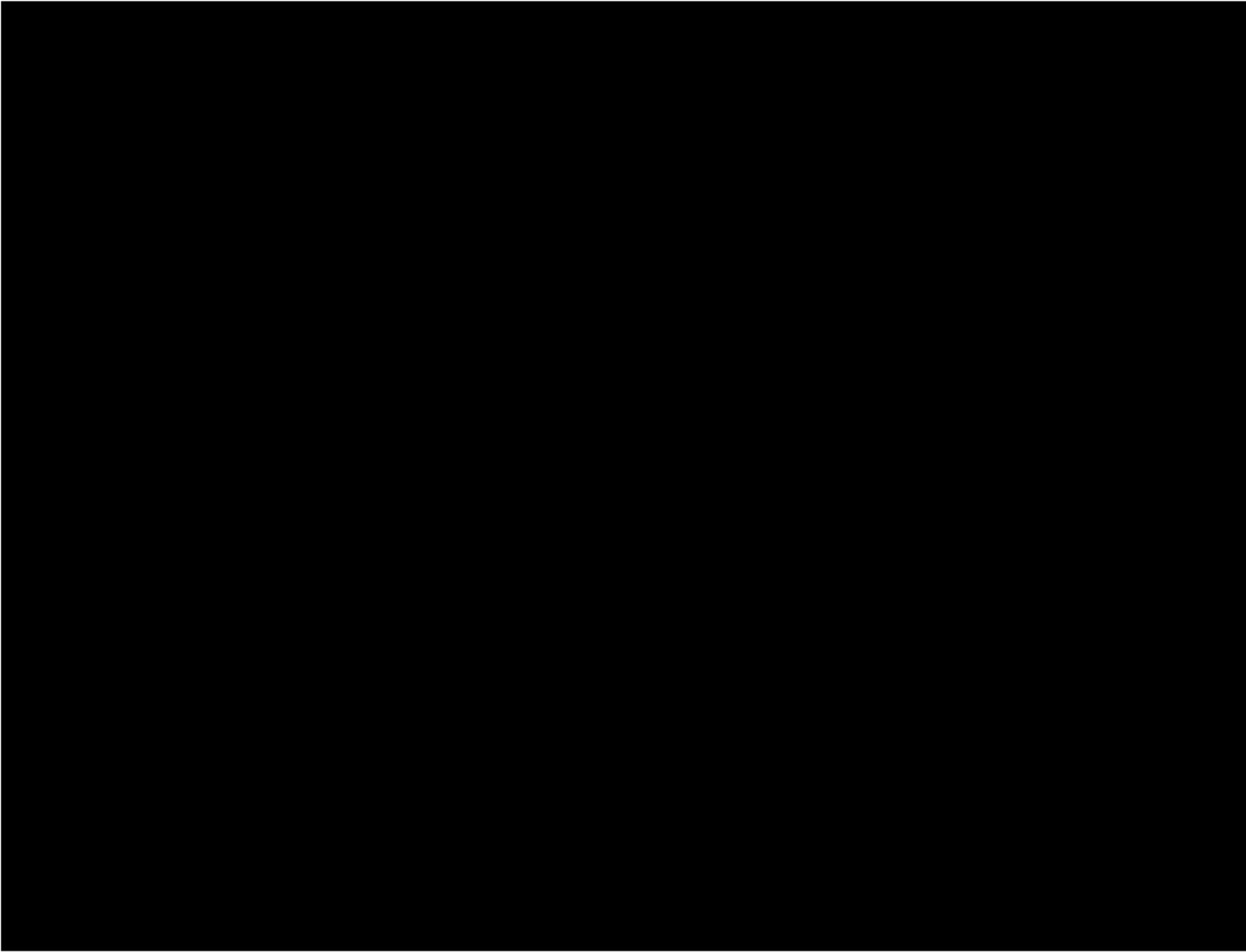
Response

have if the treatment had been in [REDACTED]...At some point – I was young and don't quite remember when – I received Children's Special Health to ease costs, which was helpful, but it did not remove the red tape I'd have to cut through relatively often. I'm thankful my mom no longer has to starve herself and I feel guilty talking about these barriers. I'd rather cut through red tape than have my mom do that again. But I feel like there has to be another option because this red tape has and does actively kill people who haven't been as lucky as me. There have been times where I ran out of refills for my insulin and a week or more passed before the pharmacy could refill my prescription. I have an Enhanced Driver's License to be able to go to Canada without a passport for events like this. There have been multiple times where I was about to make the 4-hour round trip drive but got access to my insulin at the last minute. If it hadn't been more my strategic planning of refills, I would have had to go. Currently, and ever since I took over the responsibility of my refills, I make sure I get my new month's supply of insulin before I actually need it. This way I know I have a safety net--but I had to create it myself and it's almost its own job. ..Going to the pharmacy for non-diabetes related reasons even gives me anxiety. There have been times that my secondary insurance as a minor wasn't billed correctly and I nearly threw up in the pharmacy drive-thru. I didn't have that much money in my bank account as a 16-year-old (or even now as a 23-year-old), but it felt wrong to ask my parents for hundreds--sometimes over a thousand if I didn't know it was misbilled--of dollars. When something went wrong with insurance and I wasn't allowed to take my insulin, I'd cry the whole drive home because I was scared. I still am scared, I just have better coping skills now...I'm currently covered under my dad's insurance and will be for a few more years. I turn 23 this November. Every year around my birthday as an adult, I get anxiety. I fear turning 26 and no longer having my dad's health insurance. I feel like a hoarder the way I get anxiety about throwing away anything to do with my diabetes, but especially insulin. I have childhood and even adult trauma from the way I've been treated regarding insulin and diabetes supplies. Even when I can afford it, sometimes that's not enough, which is one of the scariest things to me. A pharmacy just not having the insulin or my doctor being on a week-long vacation can send me to the hospital or another country seeking help. The fact that that happens terrifies me just as much as the idea of just not being able to afford it. ..In my additional materials, I've added pictures of just before/after my diagnosis, beginning treatment, after switching to an analog insulin, and after getting an insulin pump to show how sick I was and how getting my blood sugar under control has helped me. The photos are in chronological order.

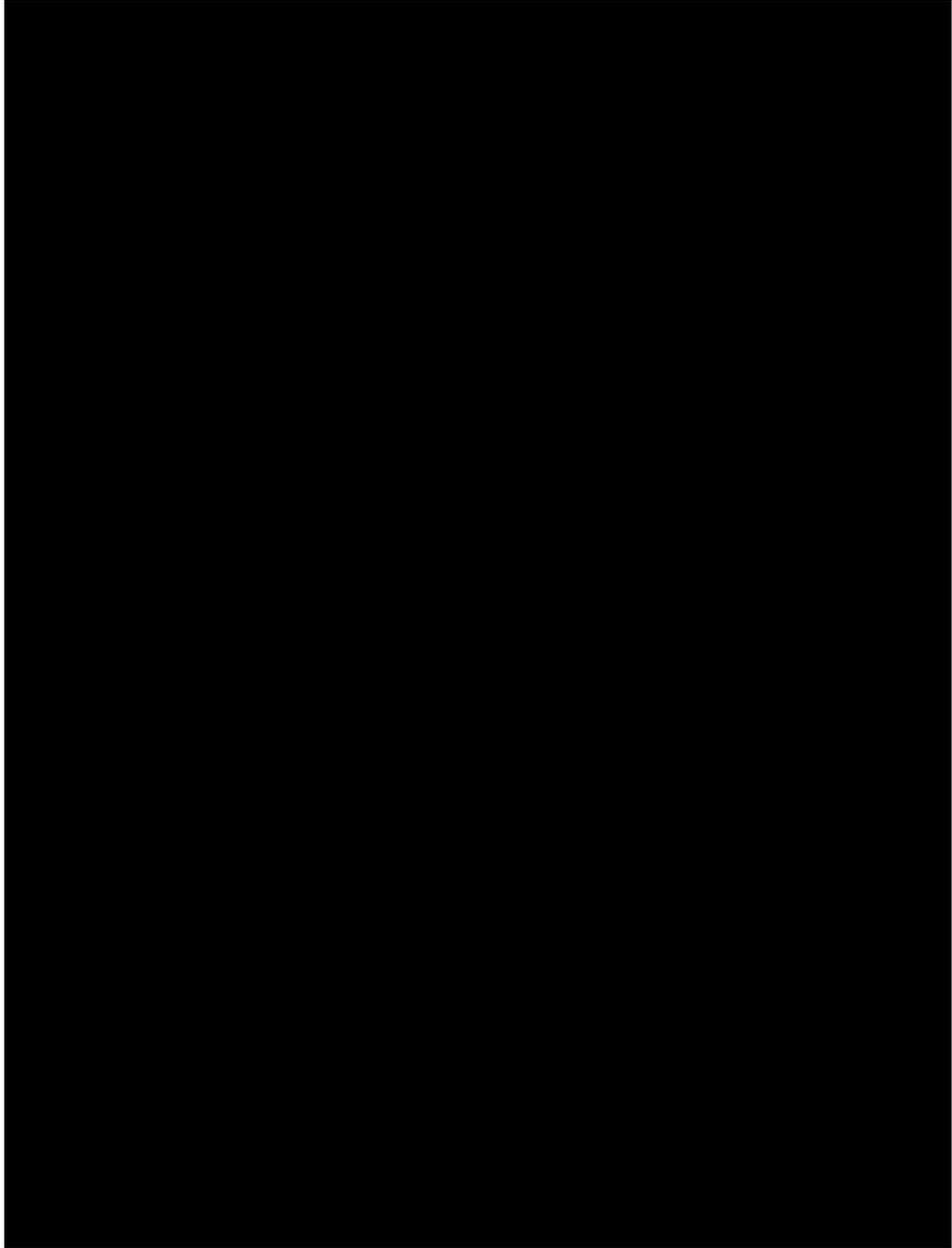
Question 32:
Executive
Summary

Response to Question 32

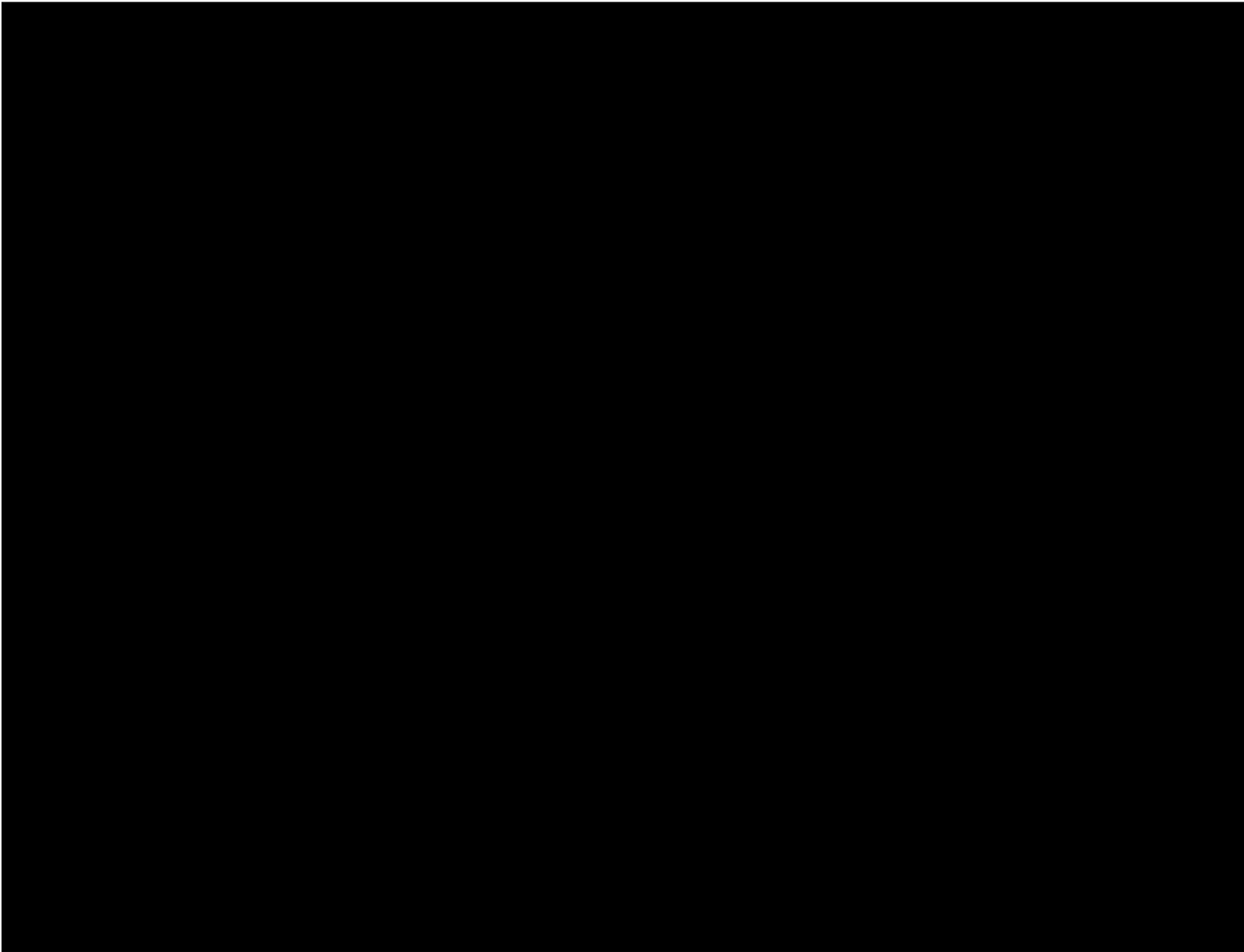






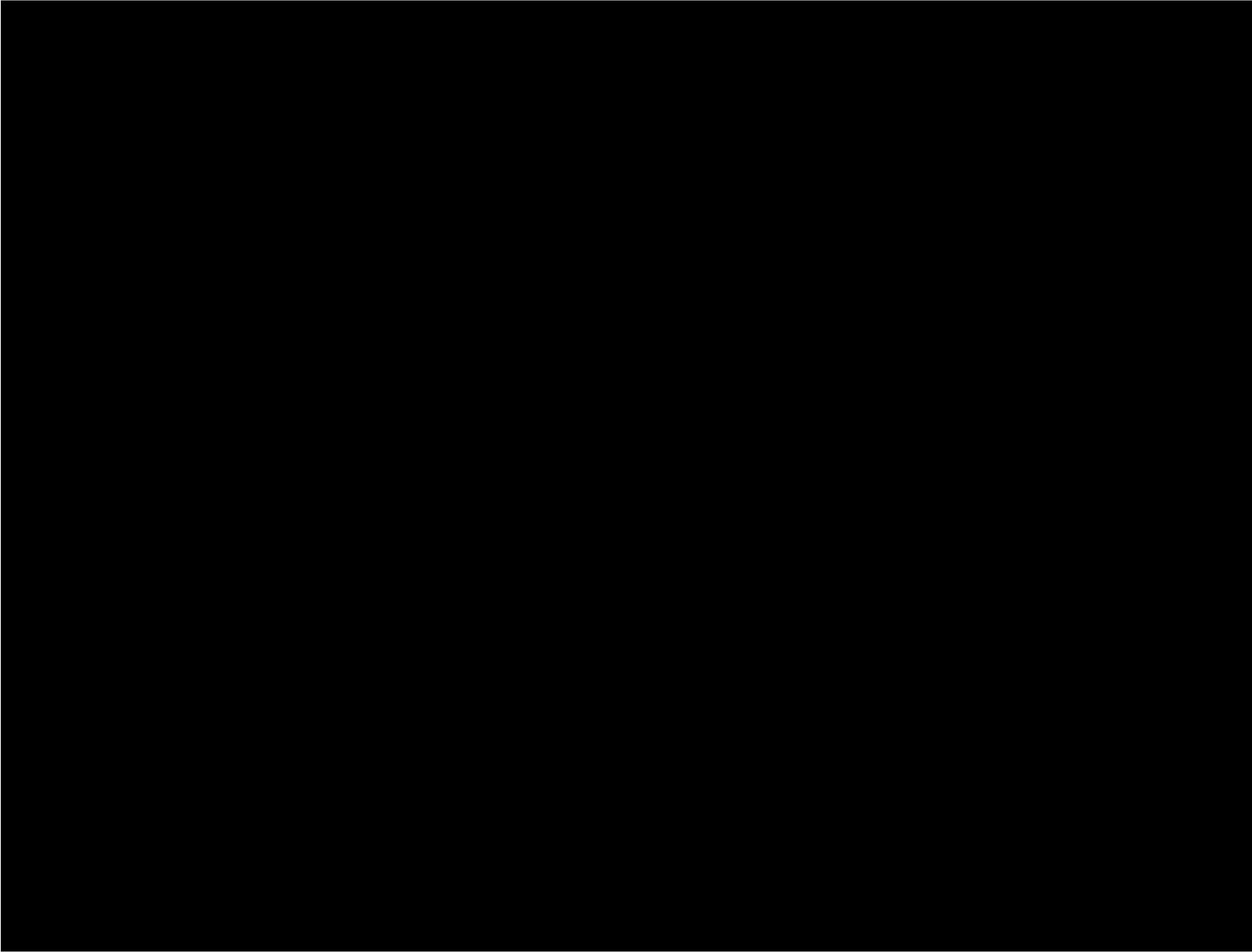












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Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	INSULIN ASPART
	Q26 - Respondent Name	
	Q26 - Organization Name (if applicable)	JDRF
	Respondent Email Who is completing this form?	PAO
Question 27: Prescribing Information	Prescribing Information	
	Evidence Submitted include a cost-effectiveness measure? What type of Evidence is shown?	
Question 28: Therapeutic Impact and Comparative Effectiveness	Therapeutic Impact and Comparative Effectiveness	<p>JDRF is the leading global organization funding type 1 diabetes (T1D) research. Our mission is to accelerate life-changing breakthroughs to cure, prevent and treat T1D and its complications and we collaborate with a wide spectrum of partners in the community to achieve this mission. Founded in 1970 by parents of children with T1D, JDRF has invested over \$2 billion in research since its inception and employs over 20 scientists to manage its research portfolio..T1D is an autoimmune disease that strikes children and adults suddenly and can be fatal. Until a cure is found and to stay alive, people with T1D require lifelong and continuous insulin therapy coupled with continuous blood sugar monitoring. Too much insulin can result in seizures, coma, or death from hypoglycemia, or low glucose levels. Too little insulin over time leads to devastating kidney, heart, nerve, and eye damage from hyperglycemia, or high glucose levels. Insulin affordability is a priority for our community because consistent access to insulin means life or death to people with T1D. .We appreciate HHS's continued focus on insulin affordability generally and through the Medicare program specifically, however, we have concerns about the coupling of 2 separate insulin aspart products on the initial negotiation list. We fear this could cause confusion among people with diabetes and potentially result in access challenges. People with diabetes consider Fiasp and Novolog as two different insulin products, as evident by their separate FDA approvals, and people with diabetes have different experiences with each drug. These differences are not trivial to people with diabetes. For example, of these products, only Novolog is approved by FDA for use in certain insulin pumps such as the Medtronic 780G, Insulet Omnipod 5 or Tandem T:slim according to FDA</p>

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Question	Sub-Question	Response
	<p data-bbox="262 966 619 1209">Hyperlink to Table/Charts/Graphs - Additional Materials for Question 28 Evidence Submitted include a cost-effectiveness measure?</p> <p data-bbox="262 1250 619 1323">What type of Evidence is shown?</p>	<p data-bbox="619 251 1969 966">approved labels for these devices. As another example of the important difference between these products, Fiasp can be given up to 20 minutes after the start of a meal, making it easier to be used by people who may not be able to predict food intake at a meal, such as toddlers, pregnant people, or people with certain comorbidities. Conversely, Novolog should be taken before a meal begins for most people with diabetes. These differences are meaningful to people who use insulin as they can make a difference in compliance and in outcomes, such as HbA1c..Due to these differences, we are concerned that targeting these separate insulin aspart products as one due to their active ingredient will reduce access to both of these drugs for people with many types of insurance, not just Medicare Part D plans. Due to the structure of the insulin out-of-pocket cap for Part D plans included in the Inflation Reduction Act, it is important that CMS ensures that treating these products as one for negotiation does not result in Part D sponsors inappropriately excluding one insulin aspart product if they cover the other. Since Fiasp and Novolog are not interchangeable or substitutable, removing one from a formulary will effectively mean that the person with diabetes will lose access to that particular insulin and any potential improvements that could come from that insulin. Experience has shown that worse health outcomes are the result when someone is denied access to an insulin product that they've utilized to successfully manage their diabetes. Access to the insulin of a patient and provider's choice is also vital to people with T1D. Using the insulin and devices that work best for the patient can lead to better glycemic control, which can reduce the risk of short- and long-term complications..We encourage CMS to ensure that patients will remain able to access both Fiasp and Novolog through Medicare Part D based on this drug negotiation process. We are ready to work with CMS to ensure that people with T1D can continue to access all FDA-approved insulins in an affordable, accessible way.</p>
	<p data-bbox="262 1372 619 1424">Response to Question 29</p>	

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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	

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

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Response

formulary requirements...3. CMS should clarify in an HPMS memo that Part D plans retain discretion on how to communicate therapeutic alternatives to enrollees, and that CMS's identification of therapeutic alternatives for purposes of the Medicare Drug Price Negotiation Program will not affect these enrollee communications...We discuss these issues in more detail below...I. CMS should identify therapeutic alternatives under the Medicare Drug Price Negotiation Program consistent with the guardrails that apply to Part D plan sponsors when identifying therapeutic alternatives for their formulary submissions. ..Currently, Part D plan sponsors consider a variety of factors when identifying therapeutic alternatives for their formulary submissions, including but not limited to (i) clinical effectiveness, (ii) safety, (iii) price, (iv) availability, and (v) patient preferences. Importantly, these factors are considered within a regulatory framework that imposes certain overarching formulary requirements. ..First, Part D plans must ensure that their formulary designs are nondiscriminatory. CMS considers several criteria when assessing whether a formulary is nondiscriminatory. CMS may presumptively approve formulary designs which align with the United States Pharmacopoeia's (USP) Medicare Model Guidelines (MMGs) based on the view that the MMGs reflect a scientifically and-clinically-based taxonomy developed by an independent expert body without a vested financial interest in the Part D program. The MMGs are also important because they provide a guiding framework for Part D plans to use when determining therapeutic alternatives. The MMGs group drugs into categories and classes. These categories and classes generally encompass the universe of potential therapeutic alternatives for a given medical condition. This means that Part D plans can use the MMGs to identify the range of therapeutic alternatives to consider when developing their formularies...Second, Part D plans must provide an adequate formulary, which among other things, means including at least two Part D drugs within a particular category or class of Part D drugs. This minimum formulary standard helps ensure a wide range of treatment options for enrollees, even if they have complex or rare medical conditions. Additionally, this requirement promotes patient choice and competition among drug manufacturers because the ability for patients to access alternative treatments incentivizes drug manufacturers to lower prices and innovate. The requirement to include at least two drugs per category or class helps to ensure that patients with a given medical condition have at least two formulary treatment options available to them, even if there are few therapeutic alternatives. This requirement is important because it prevents Part D plans from excluding entire categories or classes of drugs from their formularies...Third, Part D plans must consider cost sharing in the development of formularies. For example, CMS could raise concerns about formularies that place drugs on high cost-sharing tiers without placing therapeutic alternatives in preferable positions. CMS has also expressed concerns about "adverse tiering" where a plan sponsor assigns most or all drugs in the same therapeutic class needed to treat a specific chronic, high-cost medical condition to a high cost-sharing tier. In short, Part D plans must consider the enrollee's share of costs for a particular drug when considering therapeutic alternatives...PCMA encourages CMS to identify therapeutic alternatives for the Medicare Drug Price Negotiation Program in the same way that Part D plans do for their formularies. This would ensure consistency in process across two closely related programs and avoid introducing multiple, confusing standards for the same underlying

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definitional term. At the very least, aligning the selection of therapeutic alternatives under the Medicare Drug Price Negotiation Program with Part D formulary submissions would give Part D plans some assurance that CMS's assessment of their formulary submissions will not be affected by CMS's own process of selecting therapeutic alternatives...II. CMS's identification of therapeutic alternatives for the Medicare Drug Price Negotiation Program should not compromise the agency's evaluation of the adequacy of Part D plan formulary design, ensuring that Medicare beneficiaries continue to have access to a broad range of affordable prescription drugs...PCMA acknowledges that CMS's identification of therapeutic alternatives under the Medicare Drug Price Negotiation Program is required by law and essential for successful drug pricing negotiations. As stated above, we urge CMS to attempt to align its selection of therapeutic alternatives with how Part D plans select therapeutic alternatives...That being said, it is important to recognize that the exercise of selecting therapeutic alternatives for the Medicare Drug Price Negotiation Program and the Part D program, while overlapping in some areas, are ultimately distinct. Selecting therapeutic alternatives for the Medicare Drug Price Negotiation Program requires unique considerations that are not fully applicable to how Part D plans identify and leverage therapeutic alternatives for formulary development. Accordingly, we do not expect CMS to perfectly align itself with Part D plan sponsor methodologies for selecting therapeutic alternatives..

.First, therapeutic alternatives are a statutory feature of the Medicare Drug Price Negotiation Program. CMS selects therapeutic alternatives when negotiating pricing for selected drugs because the statute requires the agency to do so. Even if the statute did not require CMS to identify therapeutic alternatives, CMS would likely need to do so because it supports the agency in carrying out its statutory mandate to negotiate a "maximum fair price" (MFP) with manufacturers. Importantly, the MFP applies in a vacuum without regards to affordability and relative competitiveness with other drugs that a beneficiary may access...By contrast, while Part D plans are required to select therapeutic alternatives for formulary submissions, Part D plans select therapeutic alternatives based on a delicate balance between clinical comparability, cost-effectiveness, and beneficiary access. Unlike CMS, which is required to focus on a single drug in isolation when assessing therapeutic alternatives, Part D plans, PBMs, and their pharmacy and therapeutics (P&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

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Question Sub-Question

Response

formulary design, coverage determination, tiering exceptions, and Part D appeals. This means that Part D plans must carefully consider all potential scenarios in which their selection of therapeutic alternatives may be challenged...Third, CMS's identification of therapeutic alternatives for purposes of the Drug Price Negotiation Program is nonpublic. CMS indicates in the Revised Guidance for the Medicare Drug Price Negotiation Program that the agency will not unilaterally disclose any information pertaining to its negotiations with manufacturers, including the therapeutic alternatives identified for such negotiations. As a result, Part D plans do not have access to the therapeutic alternatives that CMS identifies for selected drugs. It would be unfair and arbitrary for CMS to evaluate Part D plan formulary submissions, including the identification of therapeutic alternatives contained in the submission, on a criteria that CMS never releases to the public. Formulary guidelines like the USP Medicare Model Guidelines provide a more predictable basis for administering a prescription drug benefit than nonpublic information. ..In short, while we urge CMS to align its methodology for selecting therapeutic alternatives as much as possible with Part D plans, we also request that CMS clarify that the therapeutic alternatives considered in the Medicare Drug Price Negotiation Program are distinct from the therapeutic alternatives that Part D plans must identify for purposes of formulary submissions and the overall administration of the prescription drug benefit. This will help ensure that Medicare beneficiaries continue to have access to a broad range of affordable prescription drugs. CMS can do this via an HPMS memo to Part D plans...III. Part D plans may continue to identify therapeutic alternatives in enrollee communications consistent with existing practices, regardless of CMS's identification of therapeutic alternatives for Medicare Drug Price Negotiation Program. ..Apart from formulary development, the issue of a drug's therapeutic alternatives also has implications on communications Part D sponsors are required to provide to enrollees. The Annual Notice of Change (ANOC) describes any changes to the plan's benefits, formularies, and costs for the upcoming year. The Evidence of Coverage (EOC) document describes the plan's benefits, coverage, and exclusions. Real-time benefit tools (RTBT) provide prescribers with information at the point-of-care on formulary and benefit information (including cost, formulary alternatives, and utilization management requirements). The monthly Explanation of Benefits (EOB) must include lower cost alternatives. ..While Part D plans are not required to include information about therapeutic alternatives in the ANOC or EOC, many voluntarily do so to help enrollees make informed decisions about their prescription drug coverage. This information is especially valuable for enrollees and prospective enrollees to fully understand the different treatment options available to them based on their unique circumstances. This transparency also promotes competition among Part D plans, as enrollees can better assess which plans are best for them. ..The RTBT and EOB rules have granted plans latitude in selecting which therapeutic alternatives would be displayed. CMS has stated that the "purpose of the beneficiary RTBT is to better inform beneficiaries about alternative medications," and thus, CMS allows "part D sponsors flexibility in implementing this requirement." For the EOB, CMS requires Part D sponsors to include lower-cost therapeutic alternatives but does not impose any specific requirements on plans on how they should identify those therapeutic alternatives...In summary, while Part D plans are required to communicate certain information to enrollees about therapeutic alternatives, CMS

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Question	Sub-Question	Response
	<p data-bbox="262 435 609 678">Hyperlink to Table/Charts/Graphs - Additional Materials for Question 28 Evidence Submitted include a cost-effectiveness measure?</p> <p data-bbox="262 719 609 784">What type of Evidence is shown?</p>	<p data-bbox="609 251 1967 427">provides plans with significant flexibility in the selection of those therapeutic alternatives. As such, CMS should explicitly clarify that the information on therapeutic alternatives that Part D plans choose to communicate to enrollees in required enrollee communications to beneficiaries and other regulatory requirements is not affected by CMS's selection of therapeutic alternatives for purposes of the Medicare Drug Price Negotiation Program.</p>
<p data-bbox="63 1109 262 1279">Question 29: Comparative Effectiveness on Specific Populations</p>	<p data-bbox="262 849 609 881">Response to Question 29</p> <p data-bbox="262 963 609 1060">Hyperlink to Citation - Additional Materials for Question 29</p> <p data-bbox="262 1166 609 1304">Hyperlink to Table/Charts/Graphs - Additional Materials for Question 29</p> <p data-bbox="262 1360 609 1458">Evidence Submitted include a cost-effectiveness measure?</p> <p data-bbox="262 1482 609 1547">What type of Evidence is shown?</p>	

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

Answers to Question #28 for Public Submission

The Pharmaceutical Care Management Association (PCMA) appreciates the opportunity to submit comments regarding the therapeutic alternatives for Insulin Aspart, Human. 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.