Medicare Drug Price Negotiation: The Complexities of Selecting Therapeutic Alternatives for Estimating Comparative Effectiveness

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Plain Language Summary

Medicare is set to negotiate the prices of ten Part D drugs. The prices and comparative effectiveness of therapeutic alternatives will inform these negotiations. In this article, we propose clinical comparators to the first 10 drugs selected. We also describe challenges that Medicare may face in selecting alternatives and outline implications for estimating comparative effectiveness.

Implications for Managed Care Pharmacy

Despite the central role that the selection of therapeutic alternatives will play in the upcoming price negotiations, the available guidance provides little detail about how the Centers for Medicare and Medicaid Services will select alternatives. The selection process will be particularly complex for drugs with multiple indications. We used Medicare claims data and published clinical guidelines to identify clinically comparable therapeutic alternatives that CMS might use for price negotiation.

Abstract

Under the 2022 Inflation Reduction Act, the Centers for Medicare and Medicaid Services (CMS) are able to negotiate prices for top-selling drugs in the Medicare Part B and D programs. In determining initial price offers, CMS will compare the prices and clinical benefits of the drugs subject to negotiation to the prices and clinical benefits of therapeutic alternatives. Despite the central role that the selection of therapeutic alternatives will play in the price negotiations, the available guidance published by CMS provides few details about how the organization will undertake this process, which will be particularly complex for drugs approved for more than one indication. To better inform the selection process, we identified all FDA-approved indications for the 10 first drugs subject to negotiation. Using 2020-2021 Medicare claims data, we identified Medicare Part D beneficiaries using each of the 10 drugs. We extracted medical claims with diagnosis codes for each of the approved indications to report the relative prevalence of use by indication for each drug. We reviewed published clinical guidelines to identify relevant therapeutic alternatives for each of the indications. We integrated the evidence on the relative prevalence of indications and clinical guidelines to propose therapeutic alternatives for each of the 10 drugs. We describe challenges that CMS may face in selecting therapeutic alternatives.

Introduction

The Inflation Reduction Act allows the Centers for Medicare and Medicaid Services (CMS) to negotiate drug prices.[1] In August 2023, CMS named the first 10 drugs subject to negotiation.[2] As part of the negotiation process, CMS will evaluate data on comparative effectiveness to estimate the net clinical benefits of the selected drugs compared to therapeutic alternatives.[3] CMS will then integrate the evidence of comparative effectiveness and of net prices of selected drugs and their alternatives to establish initial price offers.

Central to the negotiation process is the selection of therapeutic alternatives. The most recent guidance provides scant detail, leaving uncertainty about the criteria for selection.[4] The guidance specifies that CMS will begin by identifying therapeutic alternatives within the same drug class before potentially considering products in other classes. CMS further explains that they will not consider costs when selecting therapeutic alternatives, and that they will consult with Food and Drug Administration (FDA) officials, clinicians, patients and patient organizations, and academic experts.[3] However, it is unclear to what extent therapeutic alternatives considered in the negotiation process will be required to be clinically comparable to the drugs selected for negotiation.

In this paper, we follow CMS guidance to identify therapeutic alternatives for the first 10 drugs subject to Medicare negotiation and describe the challenges that CMS might face in the process. Appropriate selection of comparators is central to the ongoing debate over how to collect, assess and incorporate comparative effectiveness evidence in the negotiation process.

Methods

We identified all FDA-approved indications for each of the first 10 drugs selected for negotiation. (**Table 1**). To understand the relative prevalence in Medicare of each of the conditions for each drug, we used 2020-2021 claims data from a 5% random sample of Medicare beneficiaries (most recent data available). We identified all Medicare beneficiaries continuously enrolled in fee-for-service parts A, B, and D and who filled a prescription in 2021 for the drugs subject to negotiation. The date of the first prescription filled in 2021 for each of the drugs subject to negotiation was defined as index date. We extracted all inpatient and outpatient claims in the 12 months prior to index date with primary diagnosis ICD-10 codes for each of the conditions each drug is approved for (list of ICD-10 codes in **Supplemental Table 1**). These analyses were performed separately for each drug, meaning that if a beneficiary filled prescriptions for two drugs subject to negotiation, they would have two index dates, each denoting the first prescription for each drug. The use of primary diagnosis codes to identify conditions may have resulted in an underestimation of the prevalence of conditions. However, this was preferred over the use of secondary codes, which could have obscured the distinction of primary conditions for which a patient received care and thus may have received prescriptions.

We identified leading US-based professional society guidelines for all conditions that drugs selected for publication were approved for.[5–18] From clinical guidelines we compiled a comprehensive list of potential therapeutic alternatives recommended for each indication for which a drug subject to negotiation is FDA-approved. From this comprehensive list of potential therapeutic alternatives, we selected a final list integrating the clinical evidence compiled, the degree of exchangeability of comparators and drugs subject to negotiation, and the relative prevalence of conditions. When needed, we consulted with board certified specialists in the clinical disciplines of relevance for the drugs subject to negotiation.

Therapeutic Alternatives

Atrial fibrillation was the most common indication among Medicare beneficiaries using apixaban (44.1%) and rivaroxaban (38.0%), the two direct oral anticoagulants selected for negotiation (**Table 1**). Both drugs are also approved for the treatment and prevention of venous thromboembolism, and deep vein thrombosis prophylaxis in patients undergoing hip or knee replacement surgery. Additionally, rivaroxaban is indicated to reduce the risk of cardiovascular events in patients with coronary artery disease or periphery artery disease. Because only oral anticoagulants are indicated for atrial fibrillation (**Supplemental Tables 2 and 3**), the proposed therapeutic alternatives included the direct oral anticoagulant dabigatran and the vitamin K antagonist warfarin (**Table 2**). Additionally, rivaroxaban and apixaban were considered as comparators for each other. The direct oral anticoagulant edoxaban was not considered a comparator due to its low utilization in Medicare[19] and its restriction of use for patients with creatinine clearance <95mL/min due to its reduced efficacy in patients with normal kidney function.[20]

Type 2 diabetes was the leading indication for the sodium-glucose cotransporter-2 (SGLT2) inhibitors empagliflozin (prevalence of 91.9%) and dapagliflozin (86.1%), which are also approved to reduce the risk of adverse outcomes in patients with heart failure (11.9% and 18.8%) and with chronic kidney disease at risk of progression (21.8% and 26.8%), **Table 1** and **Supplemental Tables 4 and 5**. Glucagon-Like Peptide-1 (GLP1) receptor agonists are the class of antidiabetic agents with the closest therapeutic profile to SGLT2 inhibitors; however, GLP1 receptor agonists are not indicated in heart failure or chronic kidney disease. For this reason, the comparators proposed for negotiation were limited to other SGLT2 inhibitors (**Table 2**).

Type 2 diabetes is the only indication for the dipeptidyl peptidase 4 (DPP-4) inhibitor, sitagliptin (**Supplemental Table 6**). Given differences in metabolic profile, efficacy, and role in therapeutics,[5] suggested comparators included other non-insulin add-on therapies, including

DPP-4 inhibitors, SGLT2 inhibitors, and GLP1 receptor agonists (**Table 2**). Metformin was not considered an alternative as it is a first-line treatment. Second-generation sulfonylureas were not considered therapeutic alternatives because they are associated with weight gain and an increased risk of hypoglycemia.[5] According to guidelines, these metabolic characteristics disqualify them from being therapeutic alternatives for individuals with high-risk of hypoglycemia or for individuals for whom weight management is indicated; these two groups of patients represent a large share of individuals with type 2 diabetes.[21]

The branded versions of insulin aspart (NovoLog and Fiasp) are rapid-acting insulin analogues indicated for glycemic control in patients with diabetes (**Supplemental Table 7**). The therapeutic profile of insulins is defined by their duration of action;[5] therefore, selected therapeutic alternatives were limited to the rapid-acting insulin analogue insulin lispro (**Table 2**). The rapid-acting insulin glulisine was not included as a therapeutic alternative due to its low utilization among Medicare beneficiaries.[19]

The combination therapy sacubitril/valsartan is also approved for a single indication, heart failure (**Supplemental Table 8**). Sacubitril/valsartan is the only angiotensin receptor neprilysin inhibitor available. Professional society guidelines recommend the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) when the use of sacubitril/valsartan is not feasible; which were selected as proposed therapeutic alternatives (**Table 2**).[7]

The tumor necrosis factor (TNF) inhibitor etanercept is approved for rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, plaque psoriasis, and ankylosing spondylitis (**Supplemental Table 9**). Rheumatoid arthritis was the predominant indication (68.6%), followed by plaque psoriasis (11.8%) (**Table 1**). Non-TNF-inhibitor biologic disease-modifying antirheumatic drugs indicated in the treatment of rheumatoid arthritis include the Interleukin (IL)-6 receptor inhibitors, anti-CD20 antibodies, and T-cell costimulatory inhibitors;[18] however, these

drugs are not approved for plaque psoriasis. As a result, selected comparators proposed for negotiation were limited to other TNF inhibitors, which are approved for both rheumatoid arthritis and plaque psoriasis.

Ustekinumab is a biologic immunomodulator that inhibits the activity of interleukin (IL)-12 and IL-23, and the only drug approved by the FDA with this mechanism of action. Ustekinumab is approved for the treatment of plaque psoriasis, psoriatic arthritics, Crohn's disease, and ulcerative colitis (**Supplemental Table 10**). Crohn's disease was the most prevalent indication among Medicare beneficiaries using ustekinumab (45.1%), followed by plaque psoriasis (36.3%), Table 1. Among the disease-modifying antirheumatic drugs available, ustekinumab therapeutic profile most closely resembles that of IL-23 inhibitors risankizumab and guselkumab. Of the two, only risankizumab is approved for the two leading indications of ustekinumab, and therefore it was selected as the only therapeutic alternative (**Table 2**).

Ibrutinib is an inhibitor of Bruton's tyrosine kinase (BTK) indicated for the treatment of chronic cell leukemia, small lymphocytic lymphoma, Waldenstrom's macroglobulinemia, and chronic graft versus host disease (**Supplemental Table 11**). Over 80% of ibrutinib users had a diagnosis of chronic cell leukemia or small lymphocytic lymphoma. Professional society guidelines differentiate the therapeutic role of BTK inhibitors in the treatment of chronic cell leukemia and small lymphocytic lymphoma from the therapeutic role of other therapeutic agents outside of class, such as CD20 antibodies.[6] For that reason, selected comparators proposed for negotiation were limited to other BTK inhibitors (**Table 2**)**.**

Implications and Complexities Associated with Selecting Therapeutic Alternatives

The selection of therapeutic alternatives is subject to some uncertainty. We followed the CMS guidance to develop a list of therapeutic alternatives, which may serve as an independent reference for the negotiation process. In undertaking this process, we applied clinical judgement

and expert opinion to make decisions in areas of high uncertainty. Our analysis illustrates key difficulties that CMS will face in the selection of comparators.

A challenge associated with the selection of therapeutic alternatives is the fact that most drugs are approved for multiple indications. We followed a conservative approach and restricted our final list of therapeutic alternatives to drugs that shared the leading indications with the selected drug. However, CMS may choose to incorporate drugs that are partial comparators to the products subject to negotiation. In identifying the leading indications, CMS will face the same obstacle as we did in our analysis—it is not possible to identify the condition for which health care providers prescribe a drug using claims data. For this reason, our data should be interpreted as the relative treated prevalence of conditions drugs are approved for among Medicare beneficiaries using drugs subject to negotiation. This may not necessarily translate to the relative prevalence of indications driving drug utilization. It is possible that during or after the CMS manufacturer meetings, the manufacturer may provide additional data on the prevalence of indications from their own monitoring systems.

Within drugs approved for a given indication, it is unclear how CMS will decide what constitutes a therapeutic alternative. Section 60.3 of Medicare's guidance document for the drug price negotiation program, which describes the methodology for developing an initial offer, states that CMS will consider *all* therapeutic alternatives and that, in cases where there may be too many, CMS may focus on the subset of alternatives that are *most* clinically comparable.[3] However, in the appendix, CMS defines therapeutic alternative as a product that is clinically comparable to the selected drug. This nuance—whether therapeutic alternatives must be clinically comparable to the drug selected for negotiation—is of major relevance to the selection of alternatives. For example, it is unquestionable that warfarin is a therapeutic alternative to rivaroxaban and apixaban in the prevention of stroke in patients with atrial fibrillation. However, it is unclear to what extent warfarin can be considered clinically comparable to rivaroxaban and apixaban, as

there are major differences in the therapeutic management of these agents—warfarin has an increased risk of intracranial bleeding and requires continuous blood monitoring for dose adjustment.[22] Consistent with the Institute for Clinical and Economic Review, we proposed warfarin as a therapeutic alternative to rivaroxaban and apixaban,[23] as we interpreted that the text in section 60.3 of the revised guidance superseded the discrepant appendix definition. It should be noted, however, that even if therapeutic alternatives need not to be clinically comparable, CMS will identify therapeutic alternatives within the same drug class before those outside of the class.[3] Thus, it is possible CMS may not select warfarin as therapeutic alternative to apixaban and rivaroxaban as it is not a direct oral anticoagulant. This decision—whether to limit therapeutic alternatives to drugs in class—will have major implications in the assessment of comparative effectiveness and the determination of the initial price offers. If CMS only uses drugs in class as therapeutic alternatives, there will be limited room for initial price offers to fall below the current net price of the drug subject to negotiation. This is because net prices of drugs within a class tend to be relatively clustered.[24–26] However, if CMS opts to use as alternatives drugs outside of class, particularly those available in generic versions or belong to comparatively cheaper or more effective drug classes, this would put downward pressure on the initial price offers. The effect of the incorporation of outside of class drugs as therapeutic alternatives will be asymmetric though—the upper bound of the range of price offers will not be extended as it is capped by the statutory ceiling.

The selection of therapeutic alternatives for sacubitril/valsartan and for ustekinumab presented particular challenges, as these were the only drugs within their respective therapeutic classes, which were defined by mechanism of action. In both cases, we followed a counterfactual approach, identifying the drugs that most closely resemble their therapeutic profile. However, CMS could conclude that the comparators we identified are too dissimilar to the selected drugs and thus not consider them to be therapeutic alternatives. In that case, CMS would not integrate

net pricing data and comparative effectiveness evidence to determine the initial price offer. Instead, CMS would follow the process outlined in the guidance for the determination of the initial price offer for a drug with no therapeutic alternatives, which would be based on the lower of the ceiling of the negotiated price or the federal supply schedule or “Big Four Agency” price.[3] CMS may face similar decisions in future iterations of the negotiation process if drugs selected for negotiation are indicated for conditions without any other treatments approved by the FDA. CMS will then need to decide between including off-label treatments recommended by clinical guidelines, as allowed in the guidance,[3] or determining that the drug subject to negotiation has no therapeutic alternatives.[3]

Our study focused on the rationale for the selection of therapeutic alternatives but did not discuss whether therapeutic alternatives are available in branded version only, or also as generic or biosimilars. Including lower priced generic and biosimilar products would increase the potential to achieve program savings. However, it should be noted that CMS explicitly stated that cost will not be considered in the selection of therapeutic alternatives. Indeed, several comparators have generic or biosimilar versions available. This is the case of warfarin, that has been available as generic since 1997, but also of dabigatran or adalimumab, which have recently seen generic or biosimilar entry. In these latter cases, brands may have still dominated price of the generic product or the price of the branded version as reference for the derivation of the initial price offer.

The main purpose for determining therapeutic alternatives to the drugs subject to negotiation is so that CMS can estimate comparative effectiveness and net prices. That is, CMS will estimate the extent to which the drug selected for negotiation is clinically superior or inferior to the identified therapeutic alternatives; this information will be used to propose a price offer that reflects that difference in clinical benefit. What remains unclear is precisely how CMS will identify, weigh, and scientifically judge the clinical evidence, select outcomes of interest for the

comparative effectiveness assessment, and integrate that information with net price and other factors to inform the initial price offer. Much like the selection of alternatives, this step remains opaque, as CMS will follow what they indicate is a ‘qualitative approach’ to the integration of data. It also remains unclear the extent to which CMS will incorporate learnings from the patient listening sessions into the selection of therapeutic alternatives. Exercises like ours will be much needed to guide CMS in the interpretation and application of the guidance in a scientifically robust manner that ensures consistency across drugs selected for negotiation.

Conclusions

Medicare is now able to negotiate prices on a limited number of drugs. CMS guidance places the integration of clinical benefit and net prices for therapeutic alternatives at the core of the negotiation process. Decisions about what constitutes a therapeutic alternative(s) and to what extent the alternative must be clinically comparable remains uncertain. and These seemingly straightforward decisions will have a major impact on the determination of the initial price offer. As CMS will not publish the list of therapeutic alternatives used in the negotiation process, analysts and policy makers will have to rely on exercises like this to predict the impact of the negotiation process, evaluate its implementation, and identify opportunities for improvement.

References

1. Yarmuth JA. *Inflation Reduction Act of 2022*.; 2022. Accessed January 19, 2023. http://www.congress.gov/

2. Medicare Drug Price Negotiation Program: Selected Drugs for Initial Price Applicability Year 2026. Published August 30, 2023. Accessed October 26, 2023. https://www.cms.gov/files/document/fact-sheet-medicare-selected-drug-negotiation-list-ipay-2026.pdf

3. Medicare Drug Price Negotiation Program: Revised Guidance, Implementation of Sections 1191 – 1198 of the Social Security Act for Initial Price Applicability Year 2026. Accessed August 7, 2023. https://www.cms.gov/files/document/revised-medicare-drug-price-negotiation-program-guidance-june-2023.pdf

4. Sullivan SD, Hernandez I, Ramsey SD, Neumann PJ. Has the Centers for Medicare & Medicaid Services Implicitly Adopted a Value Framework for Medicare Drug Price Negotiations? *Value Health*. Published online October 21, 2023. doi:10.1016/j.jval.2023.10.004

5. ElSayed NA, Aleppo G, Aroda VR, et al. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes-2023. *Diabetes Care*. 2023;46(Suppl 1):S140-S157.

6. Eichhorst B, Robak T, Montserrat E, et al. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2021;32(1):23-33.

7. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American

Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;145(18):e895-e1032.

8. National Comprehensive Cancer Network Guidelines for Patients Graft-Versus-Host Disease. Published September 30, 2021. Accessed October 31, 2023. https://www.nccn.org/patients/guidelines/content/PDF/GVDH-patient-guideline.pdf

9. Feuerstein JD, Isaacs KL, Schneider Y, et al. AGA Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis. *Gastroenterology*. 2020;158(5):1450-1461.

10. Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. ACG Clinical Guideline: Management of Crohn's Disease in Adults. *Am J Gastroenterol*. 2018;113(4):481-517.

11. Joint American Academy of Dermatology–National Psoriasis Foundation Guidelines of care for the management and treatment of psoriasis. Accessed October 31, 2023. https://www.aad.org/member/clinical-quality/guidelines/psoriasis

12. Singh JA, Guyatt G, Ogdie A, et al. 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis. *Arthritis Rheumatol*. 2019;71(1):5-32.

13. Ward MM, Deodhar A, Gensler LS, et al. 2019 Update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis. *Arthritis Rheumatol*. 2019;71(10):1599-1613.

14. Onel KB, Horton DB, Lovell DJ, et al. 2021 American College of Rheumatology Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Oligoarthritis,

Temporomandibular Joint Arthritis, and Systemic Juvenile Idiopathic Arthritis. *Arthritis Rheumatol*. 2022;74(4):553-569.

15. Navaneethan SD, Zoungas S, Caramori ML, et al. Diabetes Management in Chronic Kidney Disease: Synopsis of the KDIGO 2022 Clinical Practice Guideline Update. *Ann Intern Med*. 2023;176(3):381-387.

16. Ortel TL, Neumann I, Ageno W, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. *Blood Adv*. 2020;4(19):4693-4738.

17. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. *Circulation*. 2019;140(2):e125-e151.

18. Fraenkel L, Bathon JM, England BR, et al. 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Care Res* . 2021;73(7):924-939.

19. Centers for Medicare & Medicaid Services. Medicare Part D Spending Dashboard. Accessed September 29, 2022. https://data.cms.gov/summary-statistics-on-use-and-payments/medicare-medicaid-spending-by-drug/medicare-part-d-spending-by-drug

20. Food and Drug Administration Highlights of Prescribing Information for Savaysa (Edoxaban). Accessed October 26, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206316lbl.pdf

21. Centers for Disease Control and Prevention (CDC). Prevalence of overweight and obesity among adults with diagnosed diabetes--United States, 1988-1994 and 1999-2002. *MMWR Morb Mortal Wkly Rep*. 2004;53(45):1066-1068.

22. Hernandez I, Zhang Y, Saba S. Comparison of the effectiveness and safety of apixaban, dabigatran, rivaroxaban, and warfarin in newly diagnosed atrial fibrillation. *Am J Cardiol*. 2017;120(10):1813-1819.

23. Institute for Clinical and Economic Review. Special Assessment to Inform CMS Drug Price Negotiation: Eliquis and Xarelto. Published October 2, 2023. Accessed October 29, 2023. https://icer.org/wp-content/uploads/2023/09/ICER_NVAF_Medicare_Assessment_100223.pdf

24. Ferris LK, Gellad WF, Hernandez I. Trends in list and net prices of self-administered systemic psoriasis therapies manufactured by US-based pharmaceutical companies. *JAMA Dermatol*. 2020;156(10):1136-1138.

25. San-Juan-Rodriguez A, Piro VM, Good CB, Gellad WF, Hernandez I. Trends in list prices, net prices, and discounts of self-administered injectable tumor necrosis factor inhibitors. *J Manag Care Spec Pharm*. 2021;27(1):112-117.

26. Hernandez I, Gabriel N, Dickson S. Estimated discounts generated by Medicare drug negotiation in 2026. *J Manag Care Spec Pharm*. 2023;29(8):868-872.

Table 1: **Relative Prevalence of Conditions for Which Drugs Subject to Negotiation are Indicated Among Part D Beneficiaries**

Medication Indication	Proportion of Medicare Part D Beneficiaries Using Medication (%)
Eliquis (apixaban), n	**3,125,087**
Non-valvular atrial fibrillation	44.1
Treatment and prevention of venous thromboembolisms	14.2
DVT prophylaxis in patients with hip or knee surgery	2.3
Xarelto (rivaroxaban), n	**1,258,010**
Non-valvular atrial fibrillation	38.0
Coronary artery disease	22.9
Treatment and prevention of venous thromboembolisms	13.7
Peripheral artery disease	8.8
DVT prophylaxis in patients with hip or knee surgery	3.6
Jardiance (empagliflozin), n	**884,516**
Type 2 diabetes	91.9
Chronic kidney disease	21.8
Heart failure	11.9
Farxiga (dapagliflozin), n	**385,693**
Type 2 diabetes	86.1
Chronic kidney disease	26.4
Heart failure	18.8
Januvia (sitagliptin), n	**934,542**
Type 2 diabetes	91.1
Fiasp (insulin aspart), n	**18,437**
Glycemic control	98.7
Novolog (insulin aspart), n	**836,931**
Glycemic control	96.3
Entresto (sacubitril-valsartan)	**394,848**
Heart failure	66.4
Enbrel (etanercept), n	**47,739**
Rheumatoid arthritis	68.6
Plaque psoriasis	11.8
Ankylosing spondylitis	4.8
Psoriatic Arthritis	4.7
Stelara (ustekinumab), n	**16,156**
Crohn's disease	45.1
Plaque psoriasis	36.3
Ulcerative colitis	12.7
Psoriatic arthritis	5.0
Imbruvica (ibrutinib), n	**26,044**
Chronic lymphocytic leukemia /small lymphocytic leukemia	81.3
Waldenstrom's macroglobulinemia	9.3
Chronic graft-versus-host disease	<1

Abbreviations: DVT=Deep Vein Thrombosis.

The table shows the number of Medicare Part D beneficiaries using the drug in 2021 according to the Medicare Part D dashboard [19] and the relative prevalence of each condition in a 5% random sample of Medicare beneficiaries.

***Table 2*: Therapeutic Alternatives per Medicare Drug and Indication**

Drug	FDA-Approved Indication	Therapeutic Alternative
Eliquis (apixaban)	Treatment and prevention of VTEs Non-valvular atrial fibrillation Treatment and prevention of stroke	Dabigatran Xarelto (rivaroxaban) Warfarin
Xarelto (rivaroxaban)	Treatment and prevention of VTEs Non-valvular atrial fibrillation Treatment and prevention of stroke Reducing the risk of CV events in CAD/PAD	Pradaxa (dabigatran) Eliquis (apixaban) Warfarin
Jardiance (empagliflozin)	Reduce the risk of CV death and hospitalizations for patients with HF Reduce the risk of CV death in patients with T2D and established CVD Adjunct therapy to diet and exercise to improve glycemic control in patients with T2D	Invokana (canagliflozin) Farxiga (dapagliflozin) Steglatro (ertugliflozin)
Farxiga (dapagliflozin)	Reduce the risk of CV death and hospitalizations for patients with HFrRF Reduce the risk of CV death in patients with T2D and established CVD or multiple cardiovascular risk factors Adjunct therapy to diet and exercise to improve glycemic control in patients with T2D Reduce the risk of sustained eGFR decline, ESRD, CV death and hospitalization for HF, in adults with CKD at risk of progression	Invokana (canagliflozin) Jardiance (empagliflozin) Steglatro (ertugliflozin)
Januvia (sitagliptin)	Adjunct to diet and exercise to improve glycemic control in patients with T2D	Onglyza (saxagliptin) Tradjenta (linagliptin) Nesina (alogliptin) Farxiga (dapagliflozin) Invokana (canagliflozin) Jardiance (empagliflozin) Steglatro (ertugliflozin) Bydureon (exenatide) Adlyxin (lixisenatide) Trulicity (dulaglutide) Victoza (liraglutide) Ozempic (semaglutide)
Fiasp & Novolog (insulin aspart)	Glycemic control for diabetes mellitus	Humalog (insulin lispro) Admelog (insulin lispro)
Entresto (sacubitril/valsartan)	Reduce the risk of CV death and hospitalization for HF in adults with CHF Treatment of symptomatic HF with systemic left ventricular dysfunction	Captopril Enalapril Lisinopril Ramipril Candesartan Losartan Valsartan
Enbrel (etanercept)	Rheumatoid arthritis Juvenile idiopathic arthritis Ankylosing spondylitis Plaque psoriasis Psoriatic arthritis	Adalimumab Cimzia (certolizumab) Infliximab Simponi (golimumab)

***Table 2* cont.**

Drug	FDA-Approved Indication	Therapeutic Alternative
Stelara (ustekinumab)	Moderate to severe plaque psoriasis	Skyrizi (risankizumab)
	Active psoriatic arthritis	
	Moderate to severe Crohn's disease	
	Moderate to severe ulcerative colitis	
Imbruvica (ibrutinib)	Chronic lymphocytic leukemia/ small lymphocytic lymphoma	Calquence (acalabrutinib) Brukinsa (zanubrutinib)
	Waldenstrom's macroglobulinemia	
	Chronic graft versus host disease	

Abbreviations: FDA=Food and Drug Administration; CV=Cardiovascular; VTE=Venous Thromboembolism, CAD=Coronary Artery Disease; PAD=Peripheral Artery Disease; T2D=Type 2 Diabetes; HF=Heart Failure; HFrRF=Heart Failure with Reduced Ejection Fraction; CHF=Chronic Heart Failure; CKD=Chronic Kidney Disease; ACE=Angiotensin-converting Enzyme; ARB=Angiotensin Receptor Blocker.