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

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INTRODUCTION

> The Inflation Reduction Act (IRA) allows the Centers for Medicare and Medicaid Services (CMS) to negotiate drug prices.[1] In August of 2023, CMS named the first 10 drugs subject to negotiation.[2]

> CMS will evaluate comparative effectiveness data of the drugs subject to negotiation compared to **therapeutic alternatives**.[3]

> CMS will integrate the evidence of comparative effectiveness and net prices of selected drugs and their **therapeutic alternatives** to establish an initial offer.

> Central to this negotiation process, is the selection of appropriate **therapeutic alternatives**.

> The guidance, written by CMS, provides scant detail in selecting **therapeutic alternatives.**[4] The following is in the guidance:

- Prioritize drugs within the same class
- Select the most clinically comparable therapeutic alternatives
- Consider brands, biologics, generics, and biosimilars

> Unclear to what extent a therapeutic alternative is considered clinically comparable, and how CMS plans to incorporate multiple indications in their negotiation process.

OBJECTIVE: Identify therapeutic alternatives for the first 10 drugs subject to Medicare negotiation and describe the challenges associated with the selection process.

METHODS

1. **Identify FDA-approved indications**

2. **Calculate the percentage breakdown of each indication in Medicare beneficiaries for the negotiated drugs**
   - 5% random sample in 2020 – 2021 claims data
   - Medicare beneficiaries continuously enrolled in FFS Part A, B, and D who had a prescription filled in 2021 for the drugs subject to negotiation
   - Extracted inpatient and outpatient claims data for 12 months prior to filling using ICD-10 codes for primary diagnosis

3. **Select therapeutic alternatives**
   - Compile a comprehensive list of potential therapeutic alternatives using US-based professional society guidelines
   - Created a final list by narrowing down using relative prevalence and clinical evidence

RESULTS

Table 1: Drugs Selected for Negotiation and their FDA – Approved Indications

Medication (generic)	Indication
ELIQUIS (APIXABAN)	**NV atrial fibrillation,** treatment and prevention of VTEs, DVT prophylaxis in patients with hip and knee surgery
XARELTO (RIVAROXABAN)	**NV atrial fibrillation,** treatment and prevention of VTE, DVT prophylaxis in patients with hip and knee surgery, coronary artery disease, peripheral artery disease
JARDIANCE (EMPAGLIFLOZIN)	**Type 2 diabetes mellitus,** heart failure, chronic kidney disease
FARXIGA (DAPAGLIFLOZIN)	**Type 2 diabetes mellitus,** heart failure, chronic kidney disease, heart failure with chronic kidney disease
JANUVIA (SITAGLIPTIN)	**Type 2 diabetes mellitus**
FIASP & NOVOLOG (INSULIN ASPART)	**Glycemic control**
ENTRESTO (SACUBITRIL-VALSARTAN)	**Heart failure**
ENBREL (ETANERCEPT)	**Rheumatoid arthritis**, plaque psoriasis, ankylosing spondylitis, psoriatic arthritis
STELARA (USTEKINUMAB)	**Crohn's disease,** plaque psoriasis, psoriatic arthritis, ulcerative colitis
IMBRUVICA (IBRUTINIB)	**CLL/SLL,** Waldenstrom's macroglobulinemia, chronic graft-versus-host disease

Bold indicates primary indication based on Table 2.

Table 3: Selected Therapeutic Alternatives to the Drugs Selected for Negotiation

ELIQUIS (APIXABAN)	XARELTO (RIVAROXABAN)	JARDIANCE (EMPAGLIFLOZIN)	FARXIGA (DAPAGLIFLOZIN)	FIASP & NOVOLOG (INSULIN ASPART)
Pradaxa (dabigatran)	Pradaxa (dabigatran)	Invokana (canagliflozin)	Invokana (canagliflozin)	Humalog (insulin lispro)
Xarelto (rivaroxaban)	Eliquis (apixaban)	Farxiga (dapagliflozin)	Jardiance (empagliflozin)	Admelog (insulin lispro)
Warfarin	Warfarin	Steglatro (ertugliflozin)	Steglatro (ertugliflozin)	

JANUVIA (SITAGLIPTIN)		ENTRESTO (SACUBITRIL-VALSARTAN)	ENBREL (ETANERCEPT)	IMBRUVICA (IBRUTINIB)
Onglyza (saxagliptin)	Bydureon (exenatide)	Captopril	Humira (adalimumab)	Calquence (acalabrutinib)
Tradjenta (linagliptin)	Adlyxin (lixisenatide)	Enalapril	Cimzia (certolizumab)	Brukinsa (zanubrutinib)
Nesina (alogliptin)	Trulicity (dulaglutide)	Lisinopril	Remicade (infliximab)	**STELARA (USTEKINUMAB)**
Farxiga (dapagliflozin)	Victoza (liraglutide)	Ramipril	Simponi (golimumab)	
Invokana (canagliflozin)	Ozempic (semaglutide)	Candesartan		Skyrizi (Risankizumab)
Jardiance (empagliflozin)		Losartan		
Steglatro (ertugliflozin)		Valsartan		

DISCUSSION

Challenges and Complexities:

1. *Integrating evidence for multiple indications per drug:*
   - Approached this conservatively and let the leading indication guide decision-making.
   - **Limitation:** it is not possible to identify a condition for which health care providers prescribe a drug using claims data.

2. *What is considered a therapeutic alternative and clinically comparable*
   - Section 60.3 states, in the case of too many therapeutic alternatives, select the most clinically comparable.
     - **E.g:** warfarin is a therapeutic alternative to apixaban and rivaroxaban, and is highly recommended in clinical guidelines, but is it considered clinically comparable? It is managed very differently in patients.
   - How to approach drugs with no therapeutic alternatives within the same class?
     - **E.g.** Stelara and Entresto; used counterfactual approach and chose therapeutic alternatives with the closest therapeutic profile.

Implications of Selecting Therapeutic Alternatives:

> The selection of therapeutic alternatives determines how the rest of the negotiation process will unfold; allowing CMS to estimate price benchmarks, estimate comparative effectiveness, and integrate this data to arrive at an initial price offer, all of which still remains unclear.

Table 2: Percentage of Medicare Beneficiaries Using Negotiated Drugs by Indication

Medication (generic) Condition for Which Medication was Prescribed	**Medicare Part D Beneficiaries Using Negotiated Drug from 5% Sample (%)***
ELIQUIS (APIXABAN), n	**3,125,087**
NV atrial fibrillation	44.1
Treatment and prevention of VTE	14.2
DVT prophylaxis	2.3
XARELTO (RIVAROXABAN), n	**1,258,010**
NV atrial fibrillation	38.0
Coronary artery disease	22.9
Treatment and prevention of VTE	13.7
Peripheral artery disease	8.8
DVT prophylaxis	3.6
JARDIANCE (EMPAGLIFLOZIN), n	**884,516**
Type 2 diabetes mellitus	91.9
Chronic kidney disease	21.8
Heart failure	11.9
FARXIGA (DAPAGLIFLOZIN), n	**385,693**
Type 2 diabetes mellitus	86.1
Chronic kidney disease	26.4
Heart failure	18.8
JANUVIA (SITAGLIPTIN), n	**934,542**
Type 2 diabetes mellitus	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), n	**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**
CLL/SLL	81.3
Waldenstrom's macroglobulinemia	9.3
Chronic graft-versus-host disease	<1

*Percentages may not add up to 100%, given that the drug may be prescribed for other conditions not listed (such as off-label use), or may exceed 100% given that the drug can be prescribed for multiple conditions.

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Abbreviations: CLL/SLL, chronic lymphocytic leukemia/small lymphocytic leukemia; CMS, Centers for Medicaid and Medicare; DVT, deep vein thromboembolism; FDA, Food and Drug Administration; FFS, Fee-For-Service; ICD, International Classification of Disease; IRA, Inflation Reduction Act; NV, non-valvular; VTE, venous thromboembolism

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