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Health Policy Analysis

Integrating Price Benchmarks and Comparative Clinical Effectiveness to Inform the Medicare Drug Price Negotiation Program

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ABSTRACT

Objectives: By September 2024, the Centers for Medicare and Medicaid Services (CMS) will publicly report the negotiated prices (Maximum Fair Prices) for the first 10 drugs selected for price negotiation. We estimate initial price offers based on net prices, statutorily defined ceilings, and comparative effectiveness data for the 10 drugs and their therapeutic alternatives.

Methods: We utilized net prices and other price benchmarks for the 10 drugs and their therapeutic alternatives. We searched for data on comparative clinical effectiveness for the primary indications. We outlined a range of plausible initial price offers based on CMS guidance and our interpretation of regulatory intent.

Results: For ibrutinib and ustekinumab, statutorily defined ceiling prices will likely determine the initial price offers. The integration of net pricing and clinical evidence from comparator branded products will inform the initial price offers for apixaban, empagliflozin, etanercept, and insulin aspart. Rivaroxaban and sacubitril/valsartan have therapeutic alternatives that are generics; therefore, CMS may apply a discount to current net prices. To achieve savings in the negotiation of dapagliflozin and sitagliptin, CMS will have to leverage additional negotiation factors because statutory defined ceilings and net prices of therapeutic alternatives are similar or higher.

Conclusions: This analysis sheds light on important price benchmarks and clinical evidence factors for the determination of the initial price offers. Although we were not able to simulate the offer and counter-offer process, our findings provide a transparent and systematic way to produce initial offers that are consistent with CMS guidance.

Keywords: CMS, Maximum Fair Price, Medicare Price Negotiation.

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Highlights

- The Centers for Medicare and Medicaid Services will publicly report the negotiated prices (Maximum Fair Prices) for the first 10 drugs selected for price negotiation.
- We report an estimate of the initial price offers to inform negotiation.
- This analysis sheds light on important price benchmarks and the integration of comparative clinical evidence for the determination of the initial price offers.

Introduction

The Centers for Medicare and Medicaid Services (CMS) will soon publish the final negotiated prices (Maximum Fair Prices, or MFPs) for the first 10 drugs selected for Medicare price negotiation. To arrive at the MFPs, CMS will follow the approach outlined in the 2022 Inflation Reduction Act and described in detail in published guidance.[1] The statute sets a ceiling for each MFP, which in the initial round of negotiation is defined as the lower of (1) the net price paid by Part D plans in 2022 or (2) the nonfederal average manufacturer price with a discount based on time since approval by the US Food and Drug Administration (FDA).

CMS will initially negotiate the prices of the single-source products that account for the highest gross spending in Medicare. The first cohort of 10 drugs was selected in late 2023 and comprises FDA-approved products used to treat patients with cardiovascular disease, diabetes, cancer, and immunologic conditions; these 10 drugs jointly accounted for more than $50 billion per year in gross Medicare spending.[2] The price negotiation phase starts with an initial price offer from CMS to the manufacturer and concludes after 2 rounds of negotiation with the published MFP. For the first cohort, the published MFPs will be available in early September 2024.

To derive the initial price offers, CMS will integrate a wide range of information. First, CMS will select therapeutic alternatives for each of the negotiated drugs.[3,4] Then, CMS will derive the initial price offer based on the statutory ceiling price imposed by law, the net prices of the drugs selected for negotiation and their therapeutic alternatives, and evidence on comparative clinical effectiveness (Appendix Fig. 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.08.001). Specifically, CMS will use the net prices of therapeutic alternatives as starting point of the initial price offer, as long as the net prices are lower than the ceiling for the MFP for the negotiated drug. This starting point of the initial price offer will then be adjusted based on clinical benefit of the selected drug compared with therapeutic alternatives. For products with no therapeutic alternatives or for therapeutic alternatives with net prices above the statutory ceiling, CMS will use the lower of the ceiling, the Big Four Federal Agency prices (Veterans Administration, Department of Defense, Public

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Health Service, and Coast Guard), or the Federal Supply Schedule price. CMS will further adjust this starting point based on unmet medical need, costs of research and development, production and distribution costs, and whether the manufacturer received any financial support from the US government before commercialization. Although the guidance clearly identifies the factors to be used in developing the initial price, there is great uncertainty about how these parameters will inform the initial price offers.

We recently reported our estimates of net prices and other price benchmarks for the first 10 selected drugs and their therapeutic alternatives.[5] Here, we extend this prior work by reporting estimates of the initial price offers for the first 10 drugs selected for negotiation by integrating comparative clinical effectiveness data when relevant—for drugs that have therapeutic alternatives with net prices below the ceiling of the MFP. We believe that these analyses can help improve transparency in the negotiation process and shed light on what evidence might contribute most substantially to the negotiated prices because CMS is not required to reveal detailed information on how they arrived at the initial price offer or the final MFPs. One caveat of this work is that we did not have access to the information that companies or other stakeholders submitted to CMS or any additional data that CMS identified to inform their initial price offers.

Methods

Selection of Therapeutic Alternatives

We utilized our published list of therapeutic alternatives,[4] which we derived based on US FDA-approved indications, an analysis of medical diagnosis for Medicare Part D beneficiaries using selected drugs, and a review of clinical guideline recommendations. For drugs to be considered therapeutic alternatives, they had to be approved for the leading indications of the drug selected for negotiation and have a similar role in therapeutics according to clinical guideline recommendations.

Price Benchmarks

We have previously outlined the various price benchmarks that CMS will consider.[5,6] These include: (1) the 2021 list price, (2) the maximum negotiated price based on the minimum statutory discount, (3) the estimated net price, (4) the ceiling of the MFP (the lower of the last 2), (5) the Big Four prices, and (6) 50% of the net price according to Congressional Budget Office projections. The minimum statutory discount was estimated as the product of the nonfederal average manufacturer price and the minimum discount based on years since FDA approval. The ceiling of the MFP is defined as the lower of the net price or the price set by statutory discount (75% of nonfederal average manufacturer price for drugs that have been on the market for 9 to 16 years and 40% for drugs that have been on the market for over 16 years). We estimated both the net prices and the nonfederal average manufacturer prices.[7] In brief, we subtracted 340B sales from gross sales for each product reported by IQVIA, which are net of direct sales channels discounts. We then amortized the remaining amount across all units of product that were not subject to 340B discounts.

For brand-name products, we reported net prices in 2021. For generic comparators, we reported gross reimbursement in Medicare Part D. We reported price benchmarks per 30-day supply equivalents except for insulin aspart, which we expressed per 100 insulin units. For ustekinumab, we estimated the price per 90mg/1ml prefilled syringe equivalents because prefilled syringes for subcutaneous use are the most common formulation in Medicare Part D and used for maintenance regimens. We excluded from our analysis the single-dose vial formulation of ustekinumab, which is used to provide an initial loading dose in Crohn's disease and ulcerative colitis and is priced differently.

Using these price benchmarks, we classified drugs according to the elements involved in the derivation of the initial price offers, per CMS guidance.[1] For products with no therapeutic alternatives or for therapeutic alternatives with net prices above the statutory ceiling, the starting point of the initial price offer will be determined as the lowest of the ceiling or the Big Four price. For products with therapeutic alternatives with net prices lower than the ceiling for the MFP of the negotiated drug, net prices of these therapeutic alternatives and comparative clinical effectiveness data will be integrated to derive the initial price offer.

Sources of Data on Comparative Clinical Effectiveness

To identify recent estimates of comparative effectiveness, we extracted relative treatment effect from pairwise comparisons reported in network meta-analyses for the primary FDA-approved indications. We searched PubMed for network meta-analyses using the following terms: "meta analys*" along with a Medical Subject Heading descriptor for "[Network Meta-Analysis]." For each search, we also included variations of the drug name, drug class, or mechanism of action, as well as the corresponding Medical Subject Heading terms when available. We screened the titles and abstracts of articles, filtering for the most highly cited articles. We used drug class as the first search term and "network meta-analysis" as the second search term. For subsequent Wed of Science searches, the drug class was replaced with the mechanism of action or variations of the name of the drug of interest.

We prioritized research that was referenced in current professional society clinical guidelines,[8-13] included the primary indication for the drugs selected for negotiation, evaluated clinically relevant efficacy and safety endpoints, were published within the last 5 years, and evaluated each drug individually rather than evaluating an entire class. Network meta-analyses were excluded if they reported treatment effects compared with placebo and not to a therapeutic alternative of interest or if they reported entire drug class treatment effects rather than individual drugs.

Clinically relevant efficacy and safety endpoints were determined using published professional society clinical guidelines.[8-13] For any selected drug without relevant network meta-analyses, head-to-head trials were pulled if referenced in the professional society clinical guidelines.[14] For apixaban and rivaroxaban, we extracted evidence ratings from a recently published assessment conducted by the US Institute for Clinical and Economic Review.[15] The literature and clinical guideline reviews described above produced a total of 10 network meta-analyses for data extraction.[14,16-24]

Comparative Clinical Effectiveness Data Extraction

From the 10 articles, we extracted separate efficacy and safety treatment effects for each selected drug and primary indication compared with the therapeutic alternatives. Treatment effects were reported as either an odds ratio, relative risk, or hazard ratio. Confidence intervals were extracted for statistical significance. If treatment effects were reported with background therapy, we prioritized drug-naive endpoints and included those with background therapy if drug-naive treatment effects were unavailable. In the case of sitagliptin, individual drug treatment effects were not available from the published literature; therefore, we estimated a dipeptidyl peptidase-4 drug class effect.[16] Efficacy and safety endpoints also were not available for individual drug comparisons among all members of this drug class, and all-cause mortality was therefore extracted.[17] Based on the effect measure

and associated confidence interval, we assigned evidence ratings using an approach adapted from the Institute for Clinical and Economic Review framework.[25] Specifically, the 2023 Institute for Clinical and Economic Review value framework has 2 axis—one axis quantifies comparative net health benefit and the second the level of certainty. For our analyses, we incorporated only ratings based on comparative net health benefit, without mapping evidence based on level of certainty. Therefore, we used 4 ratings representing comparative net health benefit: "A" representing substantial net health benefit, "B" small net health benefit, "C" comparable net health benefit, and "D" negative net health benefit.[25] We then validated our evidence ratings with the recommendations from clinical guidelines, ensuring that the comparative clinical effectiveness evidence matched key recommendations for each drug and indication. The resulting data are presented in Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.08.001.

Integration of Price and Clinical Effectiveness

Language in the revised CMS guidance makes clear that the agency intends to retain negotiation flexibility by utilizing a qualitative approach to integrating pricing and clinical benefit data in the formulation of the initial price offer.[1] CMS further indicates that such a qualitative approach would allow nuanced differences between drugs to be reflected in the negotiation process through the adjustment of the starting point of the initial price offer derived using price benchmarks. In our approach, we used the evidence ratings described above to approximate the magnitude of the comparative net clinical benefit for the integration of price and clinical benefit. Then, we incorporated this degree of clinical benefit in the adjustment of the initial price offering in those cases which the resulted adjustment fell below the ceiling of the selected drug. Ratings of B, representing that the selected drug had a small net benefit, translated into price premiums in comparison with therapeutic alternatives. To determine the magnitude of these price premiums, we followed a market-based approach in cases which comparators were brand-name drugs. Specifically, we applied the relative difference in net price observed before negotiation to derive price offers that were reflective of differences in net clinical benefit. This approach was not deemed feasible for cases which generic products served as therapeutic alternatives because prices are not reflective of clinical value recognized in price negotiations between payers and manufacturers but rather of the competitive nature of the generic market. In the cases which selected products had a small net benefit in comparison with the therapeutic alternatives available in generic form, we specified price reductions of 20% off the net price of the product selected for negotiation. The incorporation of a price reduction off the net price of the product selected for negotiation as opposed to a price premium applied to the price of the comparator was driven by the contextualization of our approach in light of that followed by international health authorities, such as the German Federal Joint Committee, which applies price premiums to branded comparator products but considers price premiums to be unlimited or unrestricted for products with generic alternatives.[26] Ratings of C did not translate to a price premium because C represents products that have comparable health net benefits. No drugs selected for negotiation received a rating of A in comparison with the therapeutic alternatives selected, and although 2 products received ratings of D, they were not deemed relevant for the derivation of the initial price offers because of the impact of other price benchmarks, as further detailed in the results section.

Results

Table 1[14-24] lists evidence ratings for drugs selected for negotiation based on the literature review described in the methods. Table 2 shows a summary of the estimated initial price offers for a 30-day supply for each of the 10 selected drugs along with our rationale.

Drugs for Which the Initial Price Offer Is Not Informed by Therapeutic Alternatives

Figure 1 shows data for drugs for which the derivation of the initial price offer will not require the integration of clinical effectiveness data. For ibrutinib, the existing net price is only marginally lower than the list price. The only therapeutic alternative identified (acalabrutinib) had a net price above the list price for ibrutinib and almost twice the ceiling price, defined by the minimum statutory discount. Based on CMS guidance, in cases which the net price of the therapeutic alternative is above the ceiling, the lowest of the ceiling or the Big Four or Federal Supply Schedule price will set the starting point of the initial price offer. The Big Four price ($6775) was lower than the estimated ceiling ($7677) and thus will constitute the starting point for the initial price offer. Ibrutinib was considered to have a negative net benefit when compared with acalabrutinib (D rating, Table 1[14-24]). We did not use comparative effectiveness evidence to adjust the initial point of the price offer for ibrutinib because the application of a market-based negative price premium compared with acalabrutinib would have resulted in an initial price offer considerably above the ceiling. In other words, if we applied the net price premium observed reflective of the superior effectiveness of acalabrutinib in the derivation of an initial price offer for ibrutinib, we would derive a price point that offers the ceiling of ibrutinib (and under no circumstances CMS can issue offers that exceed the ceiling).

Prices for ustekinumab are dose-dependent and vary by indication. The ustekinumab prices are for the most common maintenance doses for the 4 main indications based on prefilled syringe for subcutaneous use, the most common formulation use in Part D (Fig. 1). Across indications, ustekinumab had a single therapeutic alternative, and its net price exceeded the statutorily defined price. The ceiling price based on the statutorily defined minimum 60% discount is lower than the Big Four price and thus will define the initial price offer (Table 2). In comparison with therapeutic alternative risankizumab, ustekinumab was considered to have a comparable net benefit in terms of efficacy for Chron's disease (C rating) but had a negative net benefit for plaque psoriasis (D rating). Just like in the case of ibrutinib, we did not use this comparative effectiveness evidence on the plaque psoriasis indication because it would have resulted in an initial price offer considerably above the ceiling.

Drugs for Which the Initial Price Offer Is Informed by Net Prices and Comparative Clinical Evidence of Branded Therapeutic Alternatives

Figure 2 reports data for drugs for which the derivation of the initial price offer will be based on the integration of clinical effectiveness and net price data for therapeutic alternatives because they compare with the drugs selected for negotiation. Both apixaban and empagliflozin have therapeutic alternatives that are being negotiated simultaneously. The current market differential in net prices for these 2 drugs and their therapeutic alternatives reflects the direction of clinical benefit because apixaban net price was 15% higher than rivaroxaban, and the clinical effectiveness evidence from the Institute for Clinical and

Table 1. Summary of evidence ratings for the 10 drugs selected for negotiation and their therapeutic alternatives.

Drug selected for negotiation	Primary indication	Endpoints	Therapeutic alternatives	Evidence rating	Source
Eliquis (apixaban)	NVAF	Efficacy: Stroke/ systemic embolism, MI Safety: Major bleeding, discontinuation	Warfarin	B	ICER[15,25] 2023
			Dabigatran	C+	ICER[15,25] 2023
			Rivaroxaban	-	-
Xarelto (rivaroxaban)			Warfarin	B	ICER[15,25] 2023
			Dabigatran	C	ICER[15,25] 2023
			Rivaroxaban	-	-
Jardiance (empagliflozin)	T2DM	Efficacy: Change in HbA1c while drug-naive Safety: Severe hypoglycemia while drug-naive	Dapagliflozin	-	-
			Canagliflozin	C	Tsapas et al,[16] 2020
			Ertugliflozin *	C	Tsapas et al,[16] 2020
Farxiga (dapagliflozin)			Empagliflozin	C	Tsapas et al,[16] 2020
			Canagliflozin	C	Tsapas et al,[16] 2020
			Ertugliflozin *	C	Tsapas et al,[16] 2020
Januvia (sitagliptin)‡	T2DM	All-cause mortality	Saxagliptin	C	Zheng et al,[17] 2018
			Linagliptin	C	Zheng et al,[17] 2018
			Alogliptin	C	Zheng et al,[17] 2018
		Efficacy: Change in HbA1c while drug-naive Safety: Severe hypoglycemia while drug-naive	Dapagliflozin	C	Tsapas et al,[16] 2020
			Canagliflozin	C	Tsapas et al,[16] 2020
			Empagliflozin	C	Tsapas et al,[16] 2020
			Ertugliflozin *	C	Tsapas et al,[16] 2020
			Exenatide	C	Tsapas et al,[16] 2020
			Lixisenatide †	C	Tsapas et al,[16] 2020
			Dulaglutide	D	Tsapas et al,[16] 2020
			Liraglutide	D	Tsapas et al,[16] 2020
			Semaglutide	PO: C; SC: D	Tsapas et al,[16] 2020
Entresto (sacubitril/ valsartan)	Heart Failure	Efficacy: Death from CV causes or first hospitalization for worsening HF Safety: Discontinuation, symptomatic hypotension	Captopril	-	-
			Enalapril §	B	McMurray et al,[14] 2014
			Lisinopril	-	-
			Ramipril	-	-
			Candesartan	-	-
			Losartan	-	-
			Valsartan	-	-
Enbrel (etanercept)	Rheumat-oid Arthritis	Efficacy: ACR50 Safety: Withdrawal due to AEs	Adalimumab	C	Singh et al,[20] 2016
			Certolizumab	C	Singh et al,[20] 2016
			Golimumab ¶	B	Singh et al,[20] 2016
			Infliximab	C	Singh et al,[18] 2017 Singh et al,[20] 2016
Stelara (ustekinumab)	Crohn's Disease	Efficacy: Induction/ Maintenance of Clinical Remission Safety: SAEs	Risankizumab#	C	Singh et al,[19] 2021
	Plaque Psoriasis	Efficacy: PASI90 Safety: SAEs	Risankizumab	D	Sbidian et al,[21] 2023

continued on next page

Table 1. Continued

Drug selected for negotiation	Primary indication	Endpoints	Therapeutic alternatives	Evidence rating	Source
Imbruvica (ibrutinib)	Chronic Lymphocytic Leukemia	Efficacy: PFS, OS, Progression or Death	Acalabrutinib	D	Davids et al,[22] 2020 Alrawashdh et al,[23] 2021 Hilal et al,[24] 2020
			Zanubrutinib	-	-

Note. This table should be read as drug selected for negotiation versus therapeutic alternative. Evidence ratings have been emulated from the ICER 2023 framework in which "A" demonstrates a substantial net health benefit, "B" demonstrates a small net health benefit, "C" demonstrates a comparable net health benefit, and "D" demonstrates a negative net health benefit.
ACR50 indicates American College of Rheumatology 50% response criteria; AE, adverse event; CV, cardiovascular; DPP-4i, dipeptidyl peptidase inhibitor; HbA1c, glycated hemoglobin; HF, heart failure; ICER, Institute for Clinical and Economic Review; MI, myocardial infarction; NVAF, non-valvular atrial fibrillation; OS, overall survival; PASI90, Psoriasis Area and Severity Index 90; PFS, progression-free survival; SAE, systemic adverse effect; SGLT-2i, sodium glucose transporter 2 inhibitor; T2DM, type-2 diabetes mellitus; PO, oral; SC, subcutaneous.
*Empagliflozin or dapagliflozin versus ertugliflozin was compared with metformin as background therapy.
†Sitagliptin versus lixisenatide was compared with metformin as background therapy.
‡Sitagliptin was compared with the SGLT-2i and other DPP-4i therapeutic alternatives as an entire drug class (ie, DPP-4i versus dapagliflozin).
§Evidence rating derived from a head-to-head trial, instead of a network meta-analysis.
¶Etanercept versus golimumab was compared with methotrexate as background therapy.
#Rating was based on efficacy data only.

Economic Review report suggested that apixaban is slightly more effective when compared with rivaroxaban.[15] When compared with dabigatran, rivaroxaban was found comparable (C rating), but apixaban was found to have a comparable or small net benefit (C+ rating), Table 1.[14-24] Through this indirect comparison, we deemed apixaban to have a small net benefit compared with rivaroxaban. Thus, we applied the net price premium observed in the market (of 15%) to the negotiated price of rivaroxaban described below to derive the initial price offer for apixaban.

The empagliflozin net price was 23% higher than dapagliflozin, which may reflect the improved clinical effectiveness evidence for cardiovascular event reduction.[13] Just like in the case of apixaban, we applied this prenegotiation differential observed in the market to the initial price offer of dapagliflozin (described below) to estimate the initial price offer for empagliflozin.

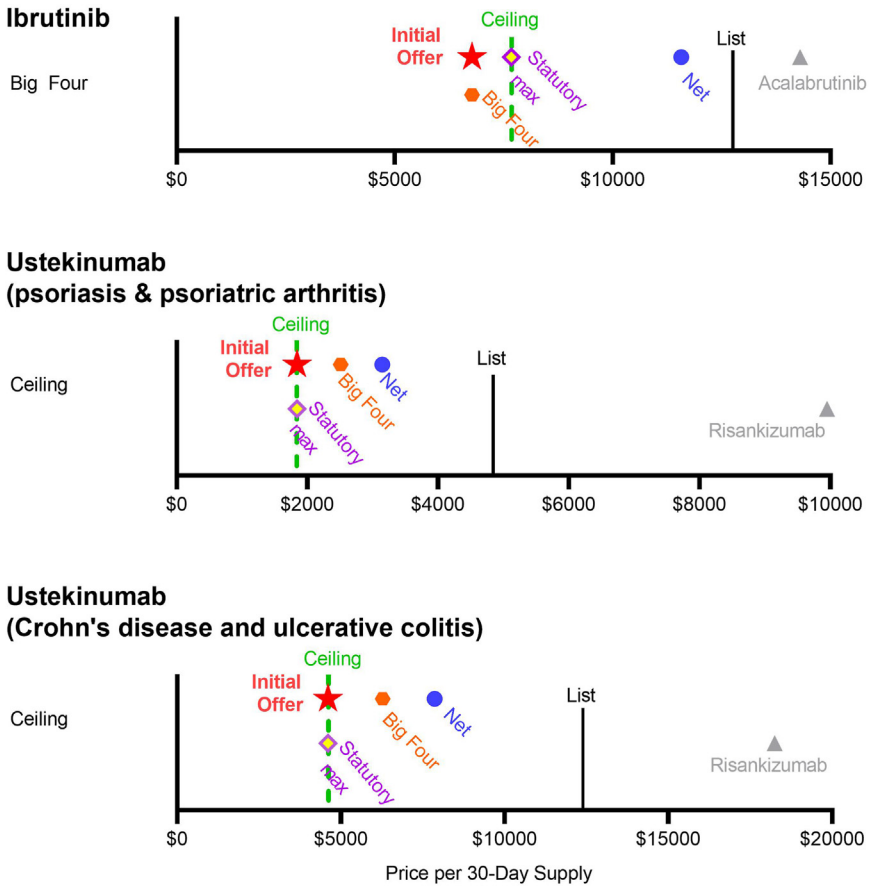
Etanercept was deemed comparable to infliximab in clinical effectiveness (C rating, Table 1[14-24]); thus, we estimated that CMS will set an initial price offer based on the existing net price of infliximab. Similarly, for insulin aspart, we estimated that CMS will set an initial price similar to the net price of insulin lispro because we assumed clinical comparability between both insulin products given the similar pharmacokinetic profile. The proposed

Table 2. Price benchmarks and estimated initial price offer.

Brand name	Generic name	list price	Net price	Big four price	Ceiling of maximum fair price	Estimated initial offer	Rationale
Imbruvica	Ibrutinib	$12 806.39	$11 571.30	$6775.20	$7677.18	$6775.20	Big Four price as therapeutic alternative has net price above ceiling
Stelara (90mg/1ml equivalent)	Ustekinumab	$24 551.55	$15 719.75	$12 554.15	$9211.95	$9211.95	Ceiling price (therapeutic alternative has net price above ceiling, and Big Four price > ceiling)
Eliquis	Apixaban	$510.51	$309.00	$90.45	$309.00	$241.31	Market-based premium of 15.4% versus negotiated rivaroxaban price
Jardiance	Empagliflozin	$558.41	$251.70	$326.40	$251.70	$190.70	Market-based premium of 23% versus negotiated dapagliflozin price
Novolog/Fiasp (100 IU/1ml equivalent)	Insulin aspart	$35.98	$12.02	$3.00	$12.02	$7.87	Net price of insulin lispro
Enbrel	Etanercept	$6435.88	$3571.61	$3254.66	$2352.65	$624.29	Net price of infliximab
Farxiga	Dapagliflozin	$545.57	$193.80	$361.80	$193.80	$155.04	80% of net price
Januvia	Sitagliptin	$505.79	$195.60	$328.50	$188.52	$156.48	80% of net price
Entresto	Sacubitril/valsartan	$597.78	$458.40	$369.00	$442.80	$366.72	80% of net price
Xarelto	Rivaroxaban	$491.97	$261.30	$328.89	$261.30	$209.04	80% of net price

Note. Big Four prices are negotiated prices for the Big Four Federal Agencies: Veterans Administration, Department of Defense, Public Health Service, and the Coast Guard. All prices are expressed per 30-day supply except for ustekinumab, which are expressed for a 90 mg/1ml prefilled syringe for subcutaneous use, and insulin aspart, which is expressed per 100 insulin units.

Figure 1. Drugs for which the initial price offer is not informed by therapeutic alternatives. The figure presents the following price benchmarks for drugs selected for negotiation: (1) list price (solid black line); (2) net price (blue circle); (3) maximum price based on the minimum statutory discount (defined on the basis of the nonfederal average manufacturer price and time since approval) (purple and yellow diamond); (4) ceiling of the negotiated price (defined as the lowest of the latter 2) (dashed green line). Gray triangles represent the net price of therapeutic alternatives. The initial price offer proposed is represented by a red star, and the main factors involved in the derivation of this initial price offer is identified in text below the drug name. All price benchmarks represent 30-day supply equivalents. For ustekinumab, price benchmarks represent maintenance doses and are shown separately for psoriasis and psoriatic arthritis and for Crohn's disease and ulcerative colitis because doses vary by indication. Prices per 30-day supply for ustekinumab were based on the pricing of the prefilled syringes for subcutaneous use because this formulation is used for maintenance regimens and the most common formulation in Medicare Part D. Price benchmarks for ustekinumab in 90 mg/1 ml prefilled syringe equivalents can be found in Table 2.



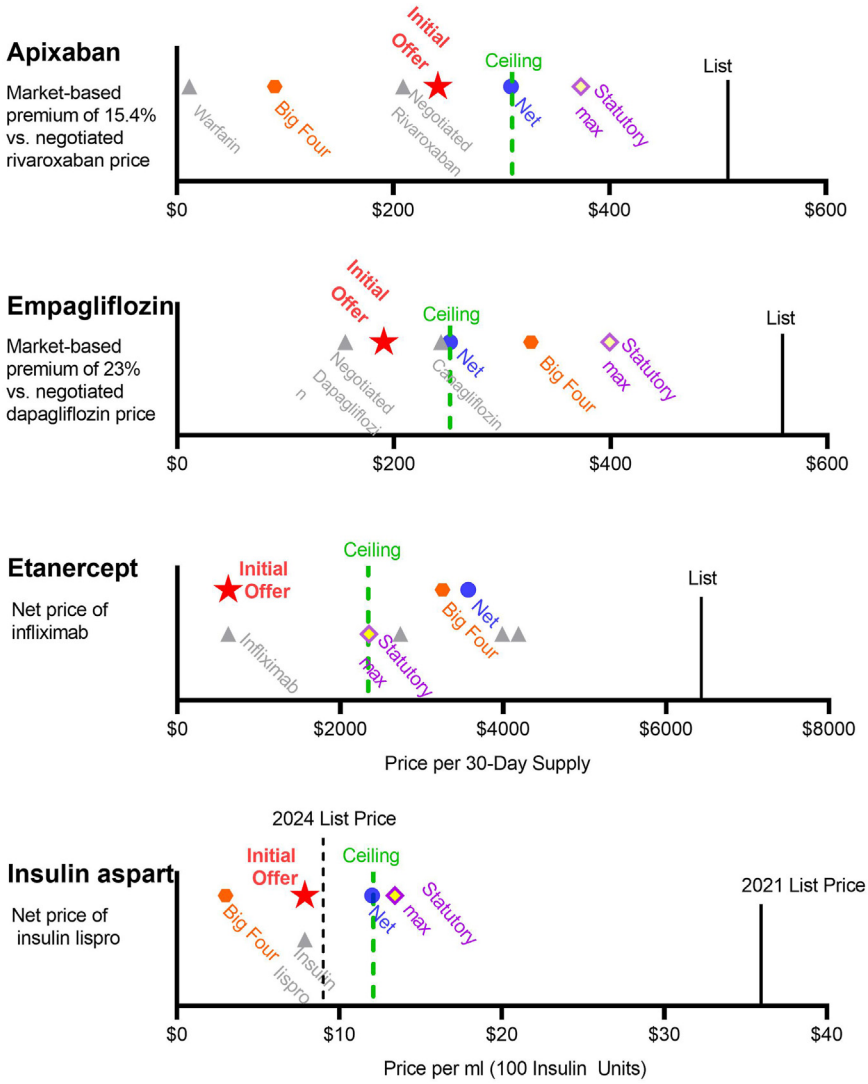
initial price offer for insulin aspart was still slightly above the 2024 list price of this product after the significant list price reductions experienced in early 2024.

Special Scenarios for the Derivation of Initial Price Offer

Figure 3 reports drugs for which we believe special considerations will play a role in the derivation of initial price offers, given the nature of therapeutic alternatives (for rivaroxaban and sacubitril/valsartan) and the lack of savings achieved using statutory ceilings and net prices of therapeutic alternatives (for dapagliflozin and sitagliptin). Rivaroxaban and sacubitril/valsartan had therapeutic alternatives with net prices considerably lower than the ceiling (Fig. 3). Although these products were identified as therapeutic alternatives, they were less likely to be considered clinically comparable to the drugs selected for negotiation and for different reasons, such as the following: (1) warfarin requires routine blood monitoring and dose adjustment, unlike new direct oral anticoagulants; (2) angiotensin-converting enzyme inhibitors and angiotensin receptor blockers play a different role in cardiovascular therapeutics compared with sacubitril/valsartan.[10] These dissimilarities between therapeutic alternatives and drugs selected for negotiation were considered in the derivation of initial price offers, which could be potentially informed by other relevant price benchmarks, circumventing the need to integrate clinical effectiveness evidence in these cases. For both products, we estimate the initial price offers to lie at 80% of the current net prices, reflective of the superior clinical profile of rivaroxaban and sacubitril/valsartan compared with the therapeutic alternatives. The net price of apixaban could not be used as the starting point of the initial price offer for rivaroxaban, because it exceeded the ceiling.

Finally, dapagliflozin and sitagliptin had net prices that were considerably lower than the minimum statutory discounts, and therapeutic alternatives had comparable or higher net prices. In this scenario, we estimate an initial price offer of 80% of the current net prices under the assumption that CMS would leverage additional factors meant to adjust the initial price offer, such as recovered research and development costs or production costs, to negotiate a MFP below the current net price. The net price of

Figure 2. Drugs for which the initial price offer is informed by net prices and comparative clinical evidence of branded therapeutic alternatives. The figure presents the following price benchmarks for drugs selected for negotiation: (1) list price (solid black line); (2) net price (blue circle); (3) maximum price based on the minimum statutory discount (defined on the basis of the nonfederal average manufacturer price and time since approval) (purple and yellow diamond); (4) ceiling of the negotiated price (defined as the lowest of the latter 2) (dashed green line). Additionally, for insulin aspart, we represent its 2024 list price after strong price reductions experienced in early 2024. Gray triangles represent the net price of therapeutic alternatives (if branded products) or gross reimbursement (if generic products). The initial price offer proposed is represented by a red star, and the main factors involved in the derivation of this initial price offer is identified in text below the drug name. All price benchmarks represent 30-day supply equivalents except for insulin aspart, which represent ml or 100 insulin units.



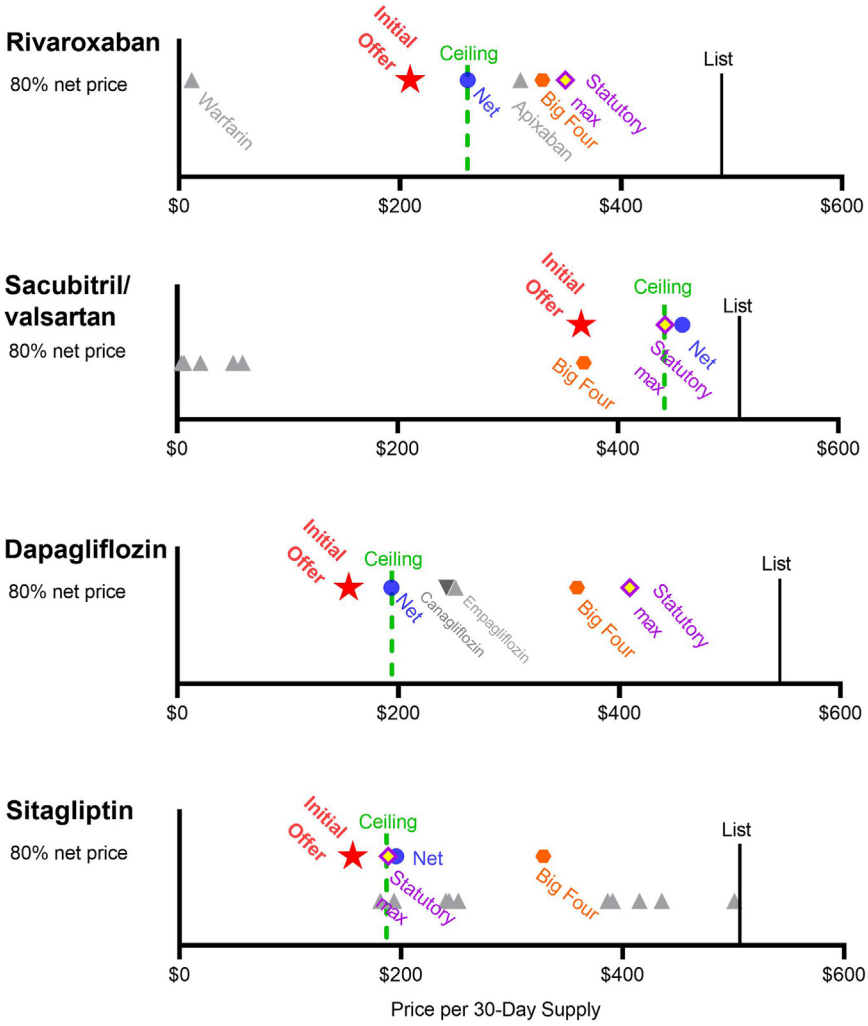
empagliflozin could not possibly be used as the starting point of the initial price offer for dapagliflozin, because it exceeded the ceiling.

Discussion

We compiled price benchmarks and comparative clinical effectiveness evidence for the first 10 drugs subject to Medicare Drug Price Negotiation to generate estimates of the initial price offers. Our approach was limited by the lack of manufacturer-submitted data, as well as the major uncertainty surrounding the selection of therapeutic alternatives by CMS and the integration of multiple data elements. Despite the important limitations of our approach, our analysis is relevant because it illustrates complexities in the interpretation of CMS guidance and the ability to follow a standardized process to derive initial price offers based on the current information made available by CMS.

Our analyses should be interpreted as an attempt to inform CMS initial price offers given context-dependent scenarios, as opposed to a prescriptive report of the process that CMS should follow in the derivation of the initial price offers. This is a critical nuance in the interpretation of our findings, which identified major sources of uncertainty in the interpretation of the guidance, as well as important difficulties encountered in the attempt to reproduce the MFPs. First, the selection of products to serve as

Figure 3. Special scenarios for the derivation of initial price offer. The figure presents the following price benchmarks for drugs selected for negotiation: (1) list price (solid black line); (2) net price (blue circle); (3) maximum price based on the minimum statutory discount (defined on the basis of the nonfederal average manufacturer price and time since approval) (purple and yellow diamond); (4) ceiling of the negotiated price (defined as the lowest of the latter 2) (dashed green line). Gray triangles represent the net price of therapeutic alternatives (if branded drugs) or gross reimbursement (if generic drugs). The initial price offer proposed is represented by a red star, and the main factors involved in the derivation of this initial price offer is identified in text below the drug name. All price benchmarks represent 30-day supply equivalents.



therapeutic alternatives plays a major role in the derivation of initial price offers in current guidance and thus introduces major uncertainty in predictions. This uncertainty stems from the unclear language used in CMS guidance on what constitutes a therapeutic alternative.[4] For instance, although some may consider warfarin a therapeutic alternative to rivaroxaban and apixaban, others may argue that these products are not clinically comparable because of the complexities in the therapeutic management of warfarin. Following peer-reviewed literature, we included warfarin in the list of therapeutic alternatives to rivaroxaban but acknowledge important dissimilarities between products in the derivation of the initial price offer.[4,15]

Second, finding a common and up-to-date source of comparative effectiveness data is problematic. Most of the published research for the selected drugs comes from industry-supported clinical development programs that preceded FDA approval. Global health technology assessment bodies are another potential source of information. These organizations frequently review evidence to support pricing and reimbursement decisions, but these assessments are typically performed at the time of product launch and therefore rely heavily on clinical data supplied by industry to support product registration. For our purposes, we found that recent clinical guidelines for the diseases treated by the 10 drugs contained the best and most recent sources of comparative clinical evidence.

Third, the guidance states that CMS will follow a qualitative approach in the integration of net price and clinical effectiveness data, without specifying measures to be used with explicit, quantitative trade-offs. Some have proposed the use of various measures for this integration, such as equal value of life years or healthy years in total.[25,27] Although we agree that these measures would enable a standardized integration of price and clinical effectiveness data across drug products, we deemed them unlikely to be used by CMS. We adopted price differentials observed in net

prices negotiated by payers before negotiation, which reflected the direction of differences in clinical effectiveness data (clinically superior drugs had higher net prices). However, this approach did not allow for consistent trade-offs across drug products because differences in net prices observed across classes may not necessarily reflect differences clinical effectiveness but rather the negotiating power of pharmacy benefit managers across scenarios. Alternatively, one could propose the use of pricing differentials based on a system of comparative effectiveness ratings, as used in France, where products are first categorized according to the magnitude of clinical benefit in comparison with their therapeutic alternatives, and then price negotiations with manufacturers follow a pattern (no price premium for comparable products, small premium for products considered to have a minor clinical benefit over the alternative, and a larger premium for products with major benefit).[28] We believe that such an approach would have resulted in relatively similar estimates for apixaban and empagliflozin because the magnitude of observed differences in net prices compared with their therapeutic alternatives is aligned with their comparative clinical benefit.

Both the French method and our market-based approach to integrating comparative effectiveness evidence with pricing data rely on the existence of a brand-name competitor to be used as reference because the application of pricing differentials with generic comparators leads to narrow price ranges. Other research teams have explored a similar approach for use by CMS.[29,30] This is the reason why the derivation of initial price offers for sacubitril/valsartan and rivaroxaban followed an alternative method. We acknowledge that our approach to integrating net pricing and clinical effectiveness was liberal because it factored in the degree to which therapeutic alternatives may be clinically comparable, whether they were branded or generic, as well as the savings achieved from the application of minimum statutory discounts. This approach may have generated internal inconsistencies because flexibilities only applied to certain products, and deviated from conventionally accepted value assessment principles, for which the same trade-offs are applied across drugs evaluated. We believe, however, that factoring in the savings achieved across different scenarios captured political factors influencing negotiations, given the pressure for the administration to demonstrate savings generated by the negotiation program, particularly in an election year.

Additionally, manufacturers of negotiated drugs will not be responsible for paying discounts off the list price in the initial (10%) and the catastrophic phase (20%), which Medicare will face instead. This is another reason why we believe that for highly rebated products, such as dapagliflozin or sitagliptin, for which statutory discounts or therapeutic alternatives are unlikely to generate savings, CMS will be forced to negotiate prices below the ceiling through the application of additional negotiation factors. Otherwise, the negotiation of MFPs that are comparable to current net prices would result in increased expenses to the Medicare program. The flexibility enabled by the "qualitative integration" approach built into CMS guidance easily allows CMS to incorporate these context-dependent and political factors into the negotiation.

Independent of political factors, the negotiation process set by CMS guidance is highly context dependent. Arguably, one of the best articulated sections of CMS guidance is 60.3, which describes the starting point of the initial price offer, based on the selection of therapeutic alternatives, their net prices, and the statutory ceiling of the negotiated price. This language clearly outlines the relevance of rebates for therapeutic alternatives in the negotiation process. The strong dependency on these market factors limits the generalizability of the findings of this first round of negotiation to future years, for which drug products selected for negotiation may be less likely to be in highly rebated competitive therapeutic classes as this first cohort of products.[31] Future research should repeat this exercise to promote transparency in the CMS process and generate lessons learned.

Limitations

In addition to the inability to estimate the impact of the offer and counter-offer process, our analysis is subject to other limitations. First, CMS will not publish the initial price offers, only the MFPs. We are, therefore, not able to validate our estimates against actual initial price offers. In other words, we will not be able to test the extent to which our deviations from the negotiated prices reported by CMS are due to differences in the derivation of the initial price offer or due to the impact of the offer/counter-offer process, which we cannot replicate. Second, we were not able to incorporate additional data elements that might be used to adjust the initial price offer, such as research and development costs, production costs, or degree of unmet need addressed by the selected drug. CMS has indicated that it is interested in patient experience to inform the negotiation process; yet, they have provided no guidance on what patient factors are important or how they might consider and weigh such factors. Third, we relied on estimates of average net prices across the commercial and Part D markets, which did not reflect differences in discounts across payers and market segments. Because of the indirect estimation of net prices based on manufacturer-reported data, we were not able to estimate net prices for products manufactured by private companies. Fourth, we limited our search of comparative effectiveness evidence to the primary indication for each product.[4] It is unclear how CMS will integrate evidence across different indications. Fifth, we were not able to estimate net prices of relevant therapeutic alternatives (specifically, dabigatran, ertugliflozin, alogliptin, lixisenatide, zanubrutinib, and insulin lispro) because of insufficient data.

Conclusion

Our analysis sheds light on how CMS might set the initial price offers following the available agency guidance. We identified 3 plausible scenarios. Through this exercise, we demonstrate the context-dependent nature of the derivation of initial price offer, as well as the specific cases in which clinical effectiveness data might play a role in the negotiation.

Author Disclosures

Author disclosure forms can be accessed below in the Supplemental Material section.

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