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Estimated Savings from Application of a Domestic Reference Price Model for Pricing Drugs at Launch, 2015-2019

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Introduction

Launch prices of new drugs are the greatest driver of increases in drug spending. We propose a limit on new drug prices called a Domestic Reference Pricing (DRP) model that limits the launch prices of new drugs based on inflation-adjusted and innovation-weighted historical launch prices of three clinically-appropriate comparators. We estimate the Medicare savings from this proposal for all new drugs approved by the Food and Drug Administration from 2015-2019.

Methods

We identified drugs approved by the Food and Drug Administration between 2015-2019. For each new drug approval, we identified clinically-appropriate comparators of similar therapeutic class, mechanism of action, and indication. The final sample included 66 new drugs matched to 128 comparator drugs. The main outcome was the domestic reference price for each new drug, which was estimated as the inflation-adjusted launch price of the comparators, weighted by the relative utilization of each comparator, and adjusted by an innovation premium based on the average time since approval for comparators. We estimated potential savings to Medicare attributed to DRPs by applying the relative differences between launch prices and DRPs to total Medicare spending for each study drug between 2015-2019.

Results

Of the 66 drugs included in analyses, 49 had a launch price higher than the DRP. The DRP represented a mean price reduction of 34 percent compared to actual launch price. Consequently, if these drugs were priced using DRP, Medicare expenditures would have been $7.0 billion lower. For the 17 drugs with launch prices below DRP, the DRP was on average 35 percent above the launch price. Likewise, if these drugs were priced at the DRP, Medicare expenditures for these drugs would have been $2.3 billion dollars greater. Overall, DRP would have reduced Medicare expenditures by $4.7 billion from 2015-2019, 18 percent of spending on these drugs. Excluding Hepatitis C

treatments, which were a rare market event, Medicare expenditures would have been $6.5 billion lower from 2015-2019, a 30 percent reduction in spending on these drugs.

Discussion

Launch price controls that limit new drug prices to historical precedents, with a presumed innovation premium, would offer significant savings to the Medicare program. Our DRP model provides a framework to limit high drug launch prices while allowing drug manufacturers to earn profits in line with historical practices.

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INTRODUCTION

Launch prices of new drugs are the greatest driver of increases in drug spending.[1] Recent efforts to address drug costs have recognized this challenge of high launch prices,[2] but policy solutions have been limited. Most approaches to limiting drug prices rely on indexing prices either to the clinical effectiveness of the drug or to prices paid in other similarly developed countries.[2, 3] New drugs, however, may not have sufficient data to calculate the relative clinical effectiveness at launch, and prices in other countries may not have been established. Instead, manufacturers may change their launch strategies to avoid setting prices in countries that would in turn, reduce U.S. prices.

To overcome these limitations, we propose a model called Domestic Reference Pricing (DRP). Our proposed model builds from earlier attempts to define a domestic reference pricing approach.[4, 5] Under this model, the price for a new drug would be based on the historical launch prices of three clinically-appropriate comparator drugs, adjusted for inflation and weighted by a presumed innovation premium based on the average age of the comparators. The presumed innovation premium is designed to offer higher rewards to new drug products in therapeutic areas dominated by older drugs while offering lower rewards to “me-too” drug products that mimic recently-approved therapies.[6] The presumed innovation premium can be calibrated by policymakers to adjust development incentives; we present three such scenarios in this analysis. The DRP would be established prior to the launch of the new drug, and the manufacturer would have the option to submit data to establish a clinical effectiveness-based price if it believed that the DRP was too low. In this paper, we model the DRP for all new drugs approved in 2015-2019 and estimate the reduction in Medicare expenditures for these drugs (exclusive of rebates), if the proposed DRP model were applied. Finally, we compare the price reductions available under domestic reference pricing to other pricing models.

METHODS

We propose a DRP pricing model where drug prices for new entrants are calculated in three stages: first, the manufacturer and the regulating body identify up to three clinically-appropriate comparator drugs for the new drug product. Second, the launch

prices of the comparator drugs are standardized to an annual treatment course for a typical patient, adjusted for inflation. The standardized price of each comparator drug is then volume-weighted based on utilization of the comparator drugs in the prior year to obtain an average price across all comparators. Third, the volume-weighted average age of the comparator drug is calculated (based on comparator drug approval dates) and used to apply a presumed innovation premium to the weighted, inflation-adjusted comparator launch price. This final price is the annual DRP for the new drug. We include a base case and two sensitivity analyses for the presumed innovation premiums applied in stage three, which would allow policymakers to balance incentives for innovation with cost controls.

Identification of New Drugs

Using the Food and Drug Administration (FDA) Orange Book, we extracted all new drug applications (NDA) approved between 2015-2019,[7] and identified trade names for type 1 or type 2 approvals (new molecular entity or new active ingredient). Using the FDA Purple Book,[8] we identified trade names for biologic drugs with first approval between 2015-2019. In this process we identified 246 new drug approvals. We excluded orphan drugs, antibiotics, and biosimilars from our analysis, as orphan drugs and antibiotics have unique development incentives, and biosimilars reference an existing drug product. The count of each type of exclusion as well as several miscellaneous exclusions are detailed in Appendix Table 1.

Identification of Comparator Drugs

Comparators were independently identified for each new drug by two investigators (L.A.B and T.N.). An electronic survey (Qualtrics, Provo, UT) was used to systematically collect information about the new drug and its potential comparators. To select comparators, the investigators first sought to identify an approved drug in the same class using the pharmacologic classes outlined by the United States Pharmacopeia.[9] After identifying FDA-approved drugs within the same therapeutic class and mechanism of action, the investigators further selected drugs with the same indication and dosage form (Appendix Figure 1). If a comparator within the same class and mechanism of

action could not be identified, a comparator with the same indication and dosage form was selected. A new drug was determined to have no comparators when there was no FDA-approved drug fitting the above criteria. Final comparators were selected after discussion to resolve discrepancies between the comparators chosen by the two investigators. The final sample included 66 new drugs matched to 128 comparator drugs (Appendix Table 2).

Analyses

We calculated the DRP in six steps. First, for each comparator identified, we selected one National Drug Code (NDC) using three criteria: age calculated using date of approval, launch price, and drug strength. In the event that one NDC was older than the rest, the NDC with the earlies approval date was selected as the comparator. If multiple NDCs were of the same age, we chose the NDC with the highest price. If both age and price were the same, we chose the NDC with the highest drug strength. After one NDC was selected for each comparator, we extracted the the NDC launch price obtained from AnalySource (reprinted with permission from First Databank). Second, we calculated the number of units for one year of treatment for each comparator drug and expressed prices per year of treatment. Third, we adjusted the comparator launch price by inflation using the consumer price index.[10] Fourth, for each comparator, we extracted the number of Medicare beneficiaries using the drug in the year immediately prior to the new drug approval.[11, 12] We then calculated the weighted average of the inflation-adjusted launch prices of comparators, using these counts of beneficiaries as weights. Fifth, for each comparator, we estimated time since approval of the comparator drug (date of approval of new drug minus the date of approval of comparator drug). Then, we estimated the weighted average time since approval for all comparators for a new drug using Medicare beneficiaries as weights. Sixth, we applied the presumed innovation premium to the weighted, inflation-adjusted comparator launch price estimated in the fourth step, which equaled a 5% premium (1.05x multiplier) for drugs with an average comparator age less than five years, a 50% premium (1.5x multiplier) for average comparator age of 5-9 years, and a 100% premium (2x multiplier) for average comparator of 10 or more years. The result is the DRP for each new drug.

We estimated reductions in Medicare expenditures on these new drugs (defined as Medicare payments to providers and pharmacies for the drugs, exclusive of any post-sale rebates) between 2015-2019.[11, 12] We calculated an annual treatment cost for each drug, using list prices from AnalySource (reprinted with permission from First Databank) annualized using the recommended dosage per FDA-approved prescribing information. For each new drug, we calculated the difference between the annual list price and the DRP. We estimated savings from the implementation of domestic reference pricing by multiplying the relative difference between the list price and the DRP and to total Medicare spending on that drug. We compared DRPs to the comparative effectiveness price estimated by the Institute for Clinical and Economic Review (ICER) at the $150,000 Quality-Adjusted Life Year (QALY) level for drugs which have a reported comparative effectiveness price.[13]

Sensitivity Analyses

In sensitivity analyses, we lowered and raised the innovation premium. In the lower innovation premium analysis, the innovation multiplier was set to 1.0 for a weighted average of 0-4 years since approval, 1.25 for 5-9 years since approval, and 1.5 for 10 or more years since approval. This simulates a least-costly alternative policy for drugs with comparators that were also recently approved. In the higher innovation premium analysis, the innovation multiplier was set to 1.25 for a weighted average of 0-4 years since approval, 2 for 5-9 years since approval, and 2.5 for 10 or more years since approval.

Some of the new drugs were also used as comparator drugs for other drug approvals (i.e., a new drug approved in 2015 was a comparator for a drug approved in 2018). When calculating the DRP for the later-approved drug, we used the DRP of the earlier-approved drug, not the observed launch price. For example, Cosentyx (secukinumab) was included as a new drug in 2015 and as a comparator drug for Siliq (brodalumab) in 2016. The actual list price of Cosentyx at launch was $44,460. The DRP was calculated to be $38,591. We calculated the DRP for Siliq (brodalumab) as if Cosentyx (secukinumab) price at launch had been the DRP ($38,591).

RESULTS

We applied the DRP to 66 new drugs approved between 2015-2019. Across all drugs, the DRP represented a mean price reduction of 16 percent compared to actual launch price. Of these 66 drugs, 49 had a launch price that was higher than the estimated DRP (Table 1). These drugs had a mean of 2.0 comparators and a mean weighted comparator age of 8.7 years. The DRP represented a mean price reduction of 34 percent compared to actual launch price. Had these drugs been priced using DRP, Medicare expenditures on these drugs would have been $7.0 billion lower over the approval period.

The mean price reduction for drugs with a DRP below launch price did not vary significantly based on the number of beneficiaries using the drug in the first year after approval (Figure 1, comparing drugs used by more than and less than 5,000 beneficiaries). However, drugs with a DRP more than 80% below actual launch price were in the <5,000 beneficiary group, suggesting that these drugs' high launch prices may have been determined in part by a small expected market. Since our analysis excluded orphan drugs, this small market is likely because of a lack of clinical utility, not clinical need.

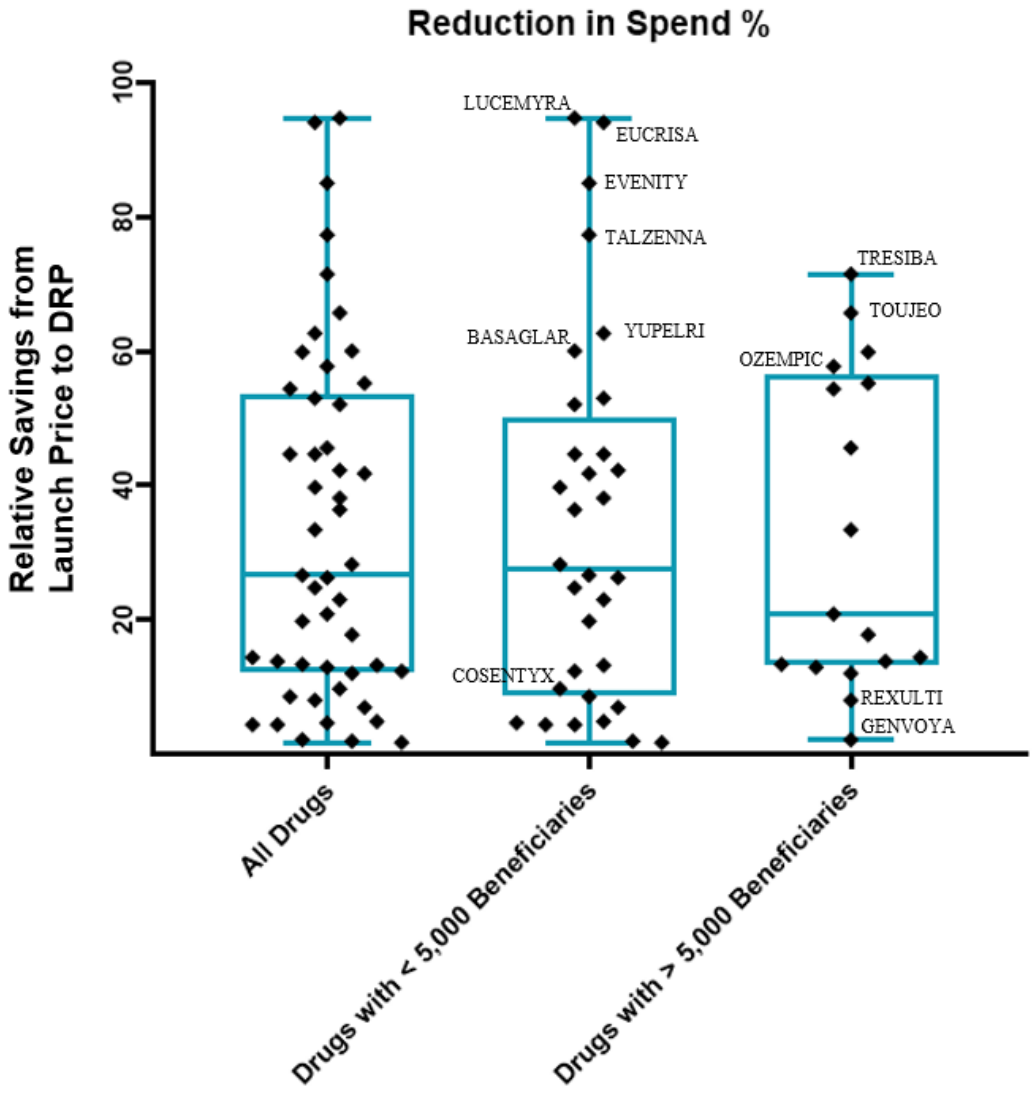
For the 17 drugs where the launch price was below the DRP, the mean number of comparators was 1.6 and the mean weighted comparator age was 5.4 years; the DRP of these drugs was on average 35 percent above the launch price. Had these drugs been priced at the DRP, Medicare expenditures on these drugs would have been $2.3 billion dollars greater. Considering drugs with DRPs lower than launch price, the overall DRP model would have reduced net Medicare expenditures by $4.7 billion between 2015-2019 (Table 1).

The greatest increase in expenditures associated with DRP were for anti-Hepatitis C agents, where DRPs were 50% above the launch prices, increasing Medicare expenditures by $1.8 billion. When anti-Hepatitis C agents were excluded from analyses, we estimated that DRP would have reduced Medicare expenditures by $6.5 billion (Table 1).

Table 1 Summary Statistics for the Overall Sample

	Base Case Analysis (n= 66)	Excluding Hepatitis C Treatments (n = 63)
Count (%) of Drugs where DRP is Below Launch Price	49 (74.24%)	49 (77.78%)
Savings for Drugs where DRP is Below Launch Price	$6,966,544,798	$6,966,544,798
Count (%) of Drugs where DRP is Above Launch Price	17 (25.76%)	14 (22.22%)
Costs for Drugs where DRP is Above Launch Price	$2,268,314,852	$434,784,782
Net Savings from Application of DRP Model	$4,698,229,946	$6,531,760,016
Net Savings from Application of DRP Model (% of Total Spending)	18.00%	30.03%

Figure 1 Relative Savings from Launch Price to DRP, per Drug



By therapeutic class, the greatest number of new drugs (12) were antineoplastic agents; these drugs had a mean weighted comparator age of 3.5 years (Table 2). The second largest therapeutic class was immunological agents; these drugs had a mean weighted comparator age of 3.82 years. Had immunological agents been priced under the DRP approach, prices would have been 16% lower, reducing Medicare expenditures by $292.6 million. The greatest reduction in expenditures was modeled in the antidiabetic agent class, where the DRP approach would have reduced expenditures by 29%, or $4.5 billion.

Table 2 Summary Statistics by Therapeutic Class

Therapeutic Class	DRP Relative to Launch, Average	Total Savings (Millions)
Anti-Addiction/Substance Abuse Treatment Agents (n= 1)	5.25%	$4.9
Antidepressants (n=1)	47.93%	$4.0
Antidiabetic Agents (n=6)	71.09%	$4,541.2
Antiemetics (n=2)	113.28%	-$2.7
Antineoplastic Agents (n=12)	91.32%	-$95.3
Antiparkinson Agents (n=2)	72.75%	$4.4
Antipsychotics (n=4)	71.16%	$677.1
Antivirals (Anti-Hepatitis C) (n=3)	150.06%	-$1,833.5
Antivirals (Anti-HIV agents) (n=2)	89.05%	$59.8
Antivirals (Anti-influenza agent) (n=1)	86.64%	$0.2
Blood Products and Modifiers (n=2)	70.49%	$5.9
Central Nervous System Agents (n=5)	74.81%	$969.4
Dermatological Agents (n=1)	5.92%	$30.7
Electrolytes/Minerals/Metals/Vitamins (n=1)	150.02%	-$3.8
Gastrointestinal Agents (n=4)	103.92%	-$0.2
Hormonal Agents (n=1)	100.81%	-$0.01
Immunological Agents (n=10)	84.40%	$292.6
Metabolic Bone Disease Agents (n=2)	40.77%	$68.8
Ophthalmic Agents (n=3)	62.67%	$113.2
Respiratory Tract/Pulmonary Agents (n=2)	107.04%	-$139.1
Sexual Disorder Agents (n=1)	90.33%	$0.4
Total (n=66)		$4,698.2

Of the 66 new drugs for which a DRP was established, we identified 16 new drugs with a comparative effectiveness price established by ICER.[14] Of these, 9 new drugs had a DRP above the ICER price at the $150k QALY threshold; these drugs had a mean price 67% greater than the ICER price. The remaining 7 drugs had a mean price 30% below the ICER price; for two of these drugs, the ICER price also exceeded the actual launch price (Table 3).

Table 3 Comparison of Domestic Reference Prices with Estimates from the Institute for Clinical and Economic Review

Brand Name	Launch Price (USD)	DRP Relative to Launch [a]	DRP Low Case Premium Relative to Launch [b]	ICER Cost Effective Price Relative to Launch [c]	Launch Pricing Date	ICER Study Date
Austedo (deutetrabenazine)	59,184.00	56.51%	47.09%	10.32% [a]	4/3/2017	12/1/2017
Cosentyx (secukinumab)	44,460.00	86.80%	72.33%	95.26%	1/30/2015	12/1/2016
Dupixent (dupilumab)	37,000.08	121.41%	101.17%	37.52%	3/28/2017	12/1/2018
Fasenra (benralizumab)	33,264.77	176.78%	132.58%	38.53%	11/14/2017	12/1/2018
Ingrezza (valbenazine tosylate)	74,700.00	44.77%	37.31%	15.07% [a]	10/5/2017	12/1/2017
Kevzara (sarilumab)	39,000.00	111.31%	92.76%	43.12% [a]	5/22/2017	4/1/2017
Mayzent (siponimod fumaric acid)	87,287.64	95.15%	79.29%	36.13%	3/26/2019	6/1/2019
Olumiant (baricitinib)	24,656.40	162.39%	135.33%	26.69% [a]	6/1/2018	4/1/2017
Orilissa (elagolix sodium)	10,983.31	100.81%	75.61%	126.26%	7/24/2018	7/1/2018
Rinvoq (upadacitinib)	59,000.04	46.98%	44.74%	75.97% [a]	8/16/2019	1/1/2020
Siliq (brodalumab)	51,987.00	61.87%	58.92%	90.81%	3/20/2017	8/1/2018
Spravato (esketamide hydrochloride)	20,060.00	47.93%	45.65%	77.78%	3/6/2019	6/1/2019
Taltz (ixekizumab)	53,347.45	77.04%	64.20%	58.99%	3/23/2016	8/1/2018
Tremfya (guselkumab)	67,788.00	57.72%	48.10%	62.59%	7/14/2017	8/1/2018
Tresiba (insulin degludec)	8,877.00	28.51%	21.38%	112.13% [a]	10/23/2015	3/1/2016
Tymlos (abaloparatide)	19,500.00	66.59%	49.94%	40.25%	5/1/2017	7/1/2017

The sensitivity analysis conducted varying innovation premiums estimated that the lower presumed innovation premiums would have resulted in a $7.7 billion reduction in Medicare expenditures, while the higher presumed innovation premiums would have resulted in a $4.4 billion increase in Medicare expenditures (Appendix Table 3).

DISCUSSION

Launch price controls that limit new drug prices to historical precedents, with a presumed innovation premium, would offer significant savings to the Medicare program. Our DRP model provides a framework to limit high drug launch prices while allowing drug manufacturers to earn profits in line with historical practices.

While our model does result in some DRPs that exceed the actual launch prices of the studied drugs, this effect is almost entirely driven by the class of curative Hepatitis C virus (HCV) treatments, which are a historical outlier. In our DRP model, the first curative HCV treatment to launch, Harvoni (ledipasvir/sofosbuvir), served as the comparator drug for subsequently approved drugs used in our analysis. However, subsequent HCV therapies launched at lower prices than Harvoni (ledipasvir/sofosbuvir), an aberration from typical drug pricing behavior in which comparative therapies that follow typically launch at higher prices. The unique nature of the HCV market and the fierce competition between brand HCV treatments likely drove this behavior,[14] and it is unlikely that the HCV treatments included in our model would have actually been priced at the higher DRP. Excluding these drugs from the analysis, the 20 drugs with DRPs above actual launch prices would only have increased Medicare expenditures by $435 million, resulting in overall savings of $6.53 billion. Antineoplastic agents account for two-thirds of these higher DRPs; the majority of these antineoplastic agents are monoclonal antibodies with only one comparator drug in our model, and the weighted mean age of the comparators for these antineoplastic agents is 3.5 years. This suggests that DRP using the main model's presumed innovation premiums may be less effective in reducing launch prices for drugs which are near first-in-class, though it would only minimally increase prices above current practices. Policymakers should consider using a lower presumed innovation premium, such as the

least-costly alternative approach considered in our sensitivity analysis, for drugs with weighted mean comparator age below five years to avoid higher launch prices.

Under the Medicare Part D program, beneficiaries are responsible for approximately 25 percent of the total cost of drugs,[15] split between out-of-pocket payments and insurance premiums. Under the Medicare Part B program, beneficiaries face 20 percent co-insurance for drugs.[16] We estimate that our DRP model would have reduced Medicare beneficiary spending by $1.2 billion between 2015-2019. These savings are already included in the total savings estimated, as the Medicare dashboard aggregate savings are inclusive of beneficiary cost-sharing. If the policy implementing DRP also extends this pricing to the commercial sector, additional savings would be realized.

Although not modeled in our analyses, our proposed DRP model would include a comparative effectiveness "escape valve" wherein a manufacturer, that believes the DRP is below the comparative effectiveness price for their drug, can demonstrate that a higher price is warranted. Of the drugs for which cost-effectiveness estimates were available, only 12.5% of would be likely to pursue this route, given that the DRP established was above the cost-effective price. While drug manufacturers currently have an incentive to delay releasing sufficient data to establish a comparative effectiveness price, the ability to justify a higher launch price with comparative effectiveness data would encourage manufacturers to design clinical trials to collect evidence on comparative effectiveness.

Overall, our DRP model would reduce spending on new drugs and likely encourage better comparative effectiveness data to be available at drug launch to justify higher prices. Our use of historical U.S. prices that do not reflect the relative clinical value of a drug means that historical overpricing is an inherent component of our model. However, we believe that this approach better constrains the launch price of new drugs compared to the current system (with no restraint) or other approaches that mandate a flat discount off the launch price,[2] as manufacturers would simply adjust their launch prices to account for the discount. Our innovation premiums based on average age of therapeutically-similar products assumes that new drugs offer an improvement over existing therapies, but it is limited in that it would over-reward drugs with no or modest

improvements and potentially under-reward drugs that represent true therapeutic breakthroughs. We include the option for a comparative-effectiveness based price to supersede the DRP to ensure that we do not discourage innovation with pricing below the value of the drug; however, our approach would likely still result in over-spending on new drugs with limited clinical value over existing therapies.

Limitations

Our analysis is subject to several limitations. First, our estimate of average annual dosing and treatment cost may vary from the actual utilization in the Medicare program, which may affect the accuracy of our estimates. Second, we limit our spending estimates to the reduction in Medicare reimbursement to pharmacies and providers, not net spending, as we cannot accurately estimate post-sale manufacturer rebates. However, given that new drugs are unexpected to have significant rebating, we believe this effect is minimal.

Conclusion

Limiting new drug launch prices using a DRP model would have reduced Medicare drug expenditures by $4.7 billion between 2015-2019, exclusive of manufacturer rebates. In addition, Medicare beneficiary spending would have been reduced by $1.2 billion. In 12.5% of new drug analyzed, the prices established under a DRP model would have exceeded cost-effectiveness pricing, ameliorating concerns that a DRP would under-reimburse innovative drugs. For the remaining 87.5% of new drugs analyzed, drug manufacturers would have the opportunity to petition for a comparative-effectiveness based price, encouraging earlier availability of clinically-relevant data.

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APPENDIX

Appendix Table 1 Exclusionary Reasons for Approved Drugs

Reason for exclusion	Number of Drugs
Admixture	2
Antibiotic	15
Antidote/reversal/rescue agent	3
Antimicrobial	4
Biosimilar	20
Diagnostic agent/test	6
No comparators	7
Not a new molecular entity	1
Not covered by part B or part D	1
Orphan	92
Parenteral nutrition	1
Radioactive drug	1
Active ingredient previously approved	2

Appendix Table 2 List of Reference and Comparator Drugs Included in the Sample

New Drugs	New Drug ATC	Comparator Drugs	Comparator Drug ATC	DRP to Launch Ratio
Adlyxin (lixisenatide)	$7,243.60	Byetta (exenatide) Trulicity (dulaglutide) Victoza (liraglutide)	$6,740.05	0.93
Akynzeo (fosnetupitant/palonosetron)	$6,630.00	Akynzeo (netupitant/palonosetron hydrochloride)	$6,520.51	0.98
Aristada (aripiprazole lauroxil)	$25,308.00	Abilify Maintena (aripiprazole)	$18,566.37	0.73
Austedo (deutetrabenazine)	$59,184.00	Xenazine (tetrabenazine)	$33,445.70	0.57
Basaglar (insulin glargine)	$6,337.00	Lantus (insulin glargine) Levemir (insulin detemir)	$2,530.39	0.40
Bevyxxa (betrixaban)	$630.00	Eliquis (apixaban) Savaysa (edoxaban) Xarelto (rivaroxaban)	$348.62	0.55
Cosentyx (secukinumab)	$44,460.00	Stelara (ustekinumab)	$38,591.24	0.87
Dupixent (dupilumab)	$37,000.08	Cosentyx (secukinumab) Stelara (ustekinumab)	$44,920.89	1.21
Epclusa (sofosbuvir/velpatasvir)	$74,760.00	Harvoni (ledipasvir/sofosbuvir)	$99,342.78	1.33
Erleada (apalutamide)	$131,040.00	Xtandi (enzalutamide)	$145,149.00	1.11
Eucrisa (crisaborole)	$6,960.00	Elidel (pimecrolimus) Kenalog (triamcinolone acetonide) Protopic (tacrolimus)	$412.30	0.06
Evenity (romosozumab-aqqg)	$21,900.00	Forteo (teriparatide) Prolia (denosumab) Tymlos (abaloparatide)	$3,275.87	0.15
Fasenra (benralizumab)	$33,264.77	Nucala (mepolizumab) Xolair (omalizumab)	$58,804.57	1.77
Genvoya (elvitegravir/cobicistat/ emtricitabine/tenofovir alafenamide)	$30,931.92	Atripla (efavirenz/emtricitabine/ tenofovir disoproxil fumarate) Complera (emtricitabine/rilpivirine/ tenofovir disoproxil fumarate) Stribild (elvitegravir/cobicistat/ emtricitabine/ tenofovir disoproxil fumarate)	$30,270.67	0.98
Ilumya (tildrakizumab-asmn)	$66,280.00	Stelara (ustekinumab)	$39,957.95	0.60
Imfinzi (durvalumab)	$135,673.59	Keytruda (pembrolizumab) Opdivo (nivolumab) Tecentriq (atezolizumab)	$159,230.43	1.17
Ingrezza (valbenazine)	$74,700.00	Xenazine (tetrabenazine)	$33,445.70	0.45
Intrarosa (prasterone)	$2,275.00	Osphena (ospemifene)	$2,054.93	0.90
Kevzara (sarilumab)	$39,000.00	Actemra (tocilizumab)	$43,412.24	1.11
Kisqali (ribociclib)	$142,350.00	Ibrance (palbociclib)	$136,149.89	0.96

Appendix Table 2 (Cont) List of Reference and Comparator Drugs Included in the Sample.

New Drugs	New Drug ATC	Comparator Drugs	Comparator Drug ATC	DRP to Launch Ratio
Libtayo (cemiplimab)	$154,700.00	Keytruda (pembrolizumab)	$162,353.36	1.05
Lokelma (sodium zirconium cyclosilicate)	$7,860.00	Veltassa (patiromer)	$11,791.48	1.50
Lonsurf (tipiracil hydrochloride/trifluridine)	$131,372.64	Stivarga (regorafenib)	$132,080.23	1.01
Lucemyra (lofexidine hydrochloride)	$1,986.24	Catapres (clonidine)	$104.22	0.05
Mayzent (glecaprevir/pibrentasvir)	$87,287.64	Gilenya (fingolimod hydrochloride)	$83,053.82	0.95
Motegrity (prucalopride succinate)	$5,086.80	Amitiza (lubiprostone) Linzess (linaclotide) Trulance (plecanatide)	$3,827.17	0.75
Nerlynx (neratinib maleate)	$126,000.00	Perjeta (pertuzumab) Tykerb (lapatinib ditosylate)	$80,173.11	0.64
Ninlaro (ixazomib citrate)	$112,710.00	Kyprolis (carfilzomib) Revlimid (lenalidomide) Velcade (bortezomib)	$110,563.78	0.98
Nourianz (istradefylline)	$18,000.00	Apokyn (apomorphine hydrochloride) Azilect (rasagiline) Xadago (safinamide)	$12,919.89	0.72
Nubeqa (darolutamide)	$138,600.00	Erleada (apalutamide) Xtandi (enzalutamide) Zytiga (abiraterone acetate)	$126,776.61	0.91
Nuplazid (pimavanserin tartrate)	$23,400.00	Abilify (aripiprazole) Fanapt (iloperidone) Seroquel (quetiapine fumarate)	$9,393.10	0.40
Ocrevus (ocrelizumab)	$65,000.00	Rituxan (rituximab) Tysabri (natalizumab)	$53,444.43	0.82
Odomzo (sonidegib phosphate)	$120,720.00	Erivedge (vismodegib)	$105,850.72	0.88
Olumiant (baricitinib)	$24,656.40	Xeljanz (tofacitinib citrate)	$40,039.89	1.62
Orilissa (elagolix sodium)	$10,983.31	Zoladex (goserelin acetate)	$11,072.48	1.01
Ozempic (semaglutide)	$17,576.00	Byetta (exenatide) Trulicity (dulaglutide) Victoza (liraglutide)	$7,429.61	0.42
Pifeltro (doravirine)	$16,560.00	Edurant (rilpivirine hydrochloride) Intelence (etravirine) Sustiva (efavirenz)	$13,288.64	0.80

Appendix Table 2 (Cont) List of Reference and Comparator Drugs Included in the Sample.

New Drugs	New Drug ATC	Comparator Drugs	Comparator Drug ATC	DRP to Launch Ratio
Plenvu (ascorbic acid/polyethylene glycol 3350/potassium chloride/sodium ascorbate/sodium chloride/sodium sulfate)	$110.00	Moviprep (polyethylene glycol 3350, sodium sulfate, sodium chloride, potassium chloride, sodium ascorbate, and ascorbic acid)	$94.84	0.86
Rexulti (brexpiprazole)	$10,386.00	Abilify (aripiprazole) Fanapt (iloperidone) Seroquel (quetiapine fumarate)	$9,555.18	0.92
Rhopressa (netarsudil mesylate)	$3,435.00	Lumigan (bimatoprost) Travatan (travoprost) Zioptan (tafluprost)	$1,566.61	0.46
Rinvoq (upadacitinib)	$59,000.04	Olumiant (baricitinib) Xeljanz (tofacitinib citrate)	$27,718.08	0.47
Savaysa (edoxaban tosylate)	$3,326.40	Eliquis (apixaban) Xarelto (rivaroxaban)	$2,848.72	0.86
Siliq (brodalumab)	$51,987.00	Cosentyx (secukinumab) Stelara (ustekinumab) Taltz (ixekizumab)	$32,163.64	0.62
Skyrizi (risankizumab)	$73,750.00	Ilumya (tildrakizumab-asmn) Stelara (ustekinumab) Tremfya (guselkumab)	$42,952.86	0.58
Spravato (esketamide hydrochloride)	$20,060.00	Abilify (aripiprazole) Rexulti (brexpiprazole)	$9,615.07	0.48
Steglatro (ertugliflozin)	$3,218.40	Farxiga (dapagliflozin propanediol) Invokana (canagliflozin) Jardiance (empagliflozin)	$6,065.92	1.88
Symproic (naldemedine tosylate)	$3,767.40	Amitiza (lubiprostone) Movantik (naloxegol) Relistor (methylnaltrexone bromide)	$6,294.99	1.67
Taltz (ixekizumab)	$53,347.45	Cosentyx (secukinumab) Stelara (ustekinumab)	$41,100.77	0.77
Talzenna (talazoparib tosylate)	$174,960.00	Lynparza (olaparib)	$39,682.28	0.23
Tecentriq (atezolizumab)	$146,540.00	Keytruda (pembrolizumab) Opdivo (nivolumab)	$157,264.59	1.07
Toujeo (insulin glargine)	$7,380.56	Lantus (insulin glargine) Levemir (insulin detemir)	$2,530.39	0.34
Tremfya (guselkumab)	$67,788.00	Stelara (ustekinumab)	$39,124.63	0.58
Tresiba (insulin degludec)	$8,877.00	Lantus (insulin glargine) Levemir (insulin detemir)	$2,530.39	0.29

Appendix Table 2 (Cont) List of Reference and Comparator Drugs Included in the Sample.

New Drugs	New Drug ATC	Comparator Drugs	Comparator Drug ATC	DRP to Launch Ratio
Trulance (plecanatide)	$4,241.76	Amitiza (lubiprostone) Linzess (linaclotide)	$3,695.25	0.87
Tymlos (abaloparatide)	$19,500.00	Forteo (teriparatide)	$12,984.87	0.67
Varubi (rolapitant hydrochloride)	$6,360.00	Emend (aprepitant)	$8,153.73	1.28
Verzenio (abemaciclib)	$142,324.00	Ibrance (palbociclib)	$136,149.89	0.96
Vosevi (sofosbuvir/velpatasvir/voxilaprevir)	$74,760.00	Epclusa (sofosbuvir/velpatasvir) Harvoni (ledipasvir/sofosbuvir) Zepatier (elbasvir/grazoprevir)	$101,179.93	1.35
Vraylar (cariprazine hydrochloride)	$12,072.96	Abilify (aripiprazole) Fanapt (iloperidone) Seroquel (quetiapine fumarate)	$9,555.18	0.79
Vumerity (diroximel fumarate)	$86,794.56	Aubagio (teriflunomide) Gilenya (fingolimod hydrochloride) Tecfidera (dimethyl fumarate)	$82,777.16	0.95
Vyzulta (latanoprostene bunod)	$2,880.00	Lumigan (bimatoprost) Travatan (travoprost) Zioptan (tafluprost)	$1,566.61	0.54
Xadago (safinamide mesylate)	$8,038.80	Azilect (rasagiline)	$5,927.10	0.74
Xiidra (lifitegrast)	$5,120.76	Restasis (cyclosporine)	$4,506.46	0.88
Xofluza (baloxavir marboxil)	$150.00	Relenza (zanamivir)	$129.96	0.87
Yupelri (revefenacin)	$12,360.00	Incruse Ellipta (umeclidinium) Spiriva (tiotropium bromide) Tudorza Pressair (aclidinium bromide)	$4,610.86	0.37
Zepatier (elbasvir/grazoprevir)	$54,600.00	Harvoni (ledipasvir/sofosbuvir)	$99,342.78	1.82

Appendix Table 3 Summary Statistics for the Sensitivity Analyses

	Low Case Analysis	**High Case Analysis**
Count (%) of Drugs where DRP is Below Launch Price	55 (83.33%)	23 (34.85%)
Savings for Drugs where DRP is Below Launch Price	$9,310,670,804	$134,831,601
Count (%) of Drugs where DRP is Above Launch Price	11 (16.67%)	43 (65.15%)
Costs for Drugs where DRP is Above Launch Price	$1,647,265,500	$4,584,083,764
Net Savings from Application of DRP (USD)	$7,663,405,303	-$4,449,252,163

Abbreviations: DRP = Domestic Reference Price

NOTES:

The two sensitivity analyses varied the innovation premium (details in the methods and sensitivity sections). The Low Case reduced the innovation premium, while the High Case increased the innovation premium. The Launch Price was calculated as the product between list price of a chosen NDC (obtained from AnalySource) and the number of units for a year worth of treatment (from the FDA approved dosing regimen). The DRP was calculated as the same product, but with utilization-weighted averages for multiple comparator drugs and adjustments for both inflation and innovation as detailed in the methods. The Savings/Costs represent the percent discount/premium obtained by going from Launch Price to DRP multiplied by the sum of total spending in the Medicare part B and part D spending dashboards for 2015-2019. Total Spending is the sum of total spending in the Medicare part B and part D spending dashboards for 2015-2019.

Appendix Figure 1 Schema for Identification of New Drug Comparators