Unsupported Price Increase Report

Unsupported Price Increases Occurring in 2022

December 11, 2023

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About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at https://icer.org/.

The funding for this report comes from non-profit foundations, with the largest single funder being the Arnold Ventures. No funding for this work comes from health insurers, pharmacy benefit managers (PBMs), or life science companies. ICER receives approximately 22% of its overall revenue from these health industry organizations to run a separate Policy Summit program, with funding approximately equally split between insurers/PBMs and life science companies. One life science company with a product included in this report, Novartis, participates in this program. For a complete list of funders and for more information on ICER's support, please visit https://icer.org/who-we-are/independent-funding/.

For drug topics, in addition to receiving recommendations from the public, ICER scans publicly available information and also benefits from a collaboration with IPD Analytics, an independent organization that performs analyses of the emerging drug pipeline for a diverse group of industry stakeholders, including payers, pharmaceutical manufacturers, providers, and wholesalers. IPD provides a tailored report on the drug pipeline on a courtesy basis to ICER but does not prioritize topics for specific ICER assessments.

The findings contained within this report are current as of the date of publication. Readers should be aware that new information may emerge following the publication of this report that could potentially influence the assessment.

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List of Acronyms and Abbreviations Used in this Report

cHL	Classical Hodgkin lymphoma
CMS	Centers for Medicare and Medicaid Services
CNS	Central nervous system
CPI	Consumer price index
FDA	Food and Drug Administration
GCCS	CogState global cognition composite score
H-ARS	Hematopoietic subsyndrome of acute radiation syndrome
HER2-	Human epidermal growth factor receptor-negative
HFmrEF	Heart failure and mildly reduced ejection fraction
HFpEF	Hart failure and preserved ejection fraction
HR	Hormone receptor
IBS-D	Irritable bowel syndrome with diarrhea
ILD	Interstitial lung disease
ITP	Immune thrombocytopenia
OS	Overall survival
PSP	Patient support program
RCT	Randomized controlled trial
6-MWD	Six-minute walk distance
TNF	Tumor necrosis factor
UPI	Unsupported price increase
US	United States
WAC	Wholesale acquisition cost

Executive Summary

The price of many existing drugs, both brand and generic, can increase substantially over time, and questions are frequently raised regarding whether these price increases are justified. State policymakers have been particularly active in seeking measures to address this issue.[1-3]

Despite these initiatives, there had been no systematic approach at a state or national level to determine whether certain price increases are justified by new clinical evidence or other factors. Starting in 2019, the Institute for Clinical and Economic Review (ICER) has published annual reports assessing whether new clinical evidence or other information has appeared that could support the price increases of drugs whose recent, substantial price increases have had the largest impact on national drug spending. This is the fifth of these reports.

Following methods similar to our prior report, we first obtained a list of the 250 drugs with the largest sales revenue in the previous calendar year (2022) in the United States (US); this information came from SSR Health LLC, an independent investment research firm. We then excluded from this list 195 drugs whose increase in wholesale acquisition cost (WAC) was not more than 2% greater than the increase in the medical consumer price index (CPI). A detailed description of the entire UPI protocol is available separately.

For each of the remaining 55 drugs, we estimated, where possible, the increase in spending in the US during 2021-2022 that was due to increases in net price as opposed to increases in volume. For the 15 drugs whose net price increases were responsible for the greatest impact on national drug spending, we asked manufacturers for early input as to whether our figures on change in net price, sales volume, and overall net revenue were correct. After applying manufacturer corrections, we generated a list of the top 10 drugs based on increase in spending in the US due to increases in net price.

As was begun in last year's report, an additional three therapies were identified that had the highest increases in total population-based spending by the Centers for Medicare and Medicaid Services (CMS) from 2020-2021 due to increases in unit prices. We needed to examine this earlier time period because of the delay in public availability of data from CMS. The decision to add a review of therapies based solely on their increase in list pricing reflected concerns ICER heard from patient groups that list price changes in Medicare Part B often have large effects on patients even if net prices do not change significantly. Overall, our protocol therefore produced a final list of 13 drugs with new evidence assessments for this year's report.

We performed assessments on these 13 drugs to determine whether there was new clinical evidence in the prior two years that demonstrated "moderate/high-quality new evidence or analyses of a substantial improvement in net health benefit compared with what was previously

believed." Drugs judged to have evidence that meets this standard are reported as having price increases "with new clinical evidence." To arrive at this judgment, ICER accepted and reviewed submissions from manufacturers of any form of evidence that could contribute to an understanding of improved net health benefit and performed our own independent systematic review of publicly available results from randomized controlled trials (RCTs). For drugs with multiple indications, evidence was sought for indications responsible for at least 10% of a drug's utilization. ICER reviewed the quality of any new evidence using the widely-accepted evidence grading system called GRADE.[4] For evidence that was felt to be high or moderate quality, ICER then assessed the magnitude of the additional net clinical benefit compared with what was previously believed.

Table ES1 on the following page shows the results of the evidence assessments. Of the 10 drugs assessed due to net price increases, eight were judged to have price increases unsupported by new clinical evidence. The unsupported net price increases of these eight drugs produced a total of $1.27 billion incremental added costs to US payers in 2022.

Of the three Medicare Part B drugs selected due to list price increases, one lacked supporting new evidence for its price increases. For this drug, patients paying 20% coinsurance under Medicare Part B would have seen an increase in individual out-of-pocket spending due just to the price increase of $684 per year.

In this year's UPI Report, two drugs appear twice. Darzalex (daratumumab) appears as one of eight drugs on the main list judged as having a price increase **unsupported** by new clinical evidence and also as one of two drugs on the separate Medicare list judged as having a price increase **with** new clinical evidence. As discussed above, the time period for price increases for the main list was 2021 to 2022 and for the Medicare list was 2020 to 2021. The evidence review looks back two years from the period of the price increase and thus the body of evidence was different in judging these two Darzalex price increases. Denosumab appears separately on the main list under its two brand names, Prolia and Xgeva. These products have different indications, dosing regimens, and pricing, and each individually had price increases that met criteria to appear on the UPI list. While the bodies of evidence differed for these two products, the price increases were both found to be unsupported by new clinical evidence.

ICER does not currently have the capacity to perform full economic analyses in conjunction with the evaluation of clinical evidence for the drugs in its UPI reports. Therefore, this UPI report does not attempt to determine whether the price increases for the three drugs with new clinical evidence were fully justified by a formal cost-effectiveness analysis. Instead, our assessment focused on whether new evidence existed that *could* justify a price increase. By identifying whether there is, or is not, new evidence of improved safety or effectiveness for drugs with substantial price increases, we hope to provide the public and policymakers with information they can use to take further steps to address drug price increases.

The Inflation Reduction Act of 2022 includes provisions addressing drug price increases beyond inflation. If a drug price increases above a broad measure of the rate of inflation (CPI-U), the marginal amount above inflation will be "clawed back" through a rebate to Medicare. How this provision will affect decisions regarding price increases for commercial payers is not clear. We will continue to examine data on drug price increases to determine whether performing assessments of new clinical evidence for drugs with substantial price increases is likely to remain relevant to policymakers and other stakeholders.

Table ES1. Drugs Selected for Assessment

Drug (Generic)	2021 to 2022 Percentage Change*		Increase in Drug Spending Due to Net Price Change (in Millions)
	WAC	Net Price	
Drugs with Price Increases Unsupported by New Clinical Evidence			
Humira (Adalimumab)	7.11%	1.95%	$386
Darzalex (Daratumumab)	6.80%	6.18%	$248
Ibrance (Palbociclib)	6.92%	4.45%	$151
Prolia (Denosumab)	7.64%	5.99%	$140
Xifaxan (Rifaxamin)	6.48%	5.83%	$98
Xgeva (Denosumab)	7.53%	7.23%	$97
Perjeta (Pertuzumab)	6.08%	6.07%	$91
Adcetris (Brentuximab Vedotin)	8.69%	8.92%	$63
Drugs with Price Increases with New Clinical Evidence†			
Jakafi (Ruxolitinib)	8.33%	5.16%	$118
Entresto (Sacubitril/Valsartan)	7.96%	2.56%	$57

Part B Drugs with Price Increases Unsupported by New Clinical Evidence		
Drug (Generic)	**2020-2021 List Price Increase**	**Additional Spending Due to Price Increase (Total Population; Per-patient§)**
Nplate (Romiplostim)	6.81%	$17 million; $684

Part B Drugs with Price Increases with New Clinical Evidence†		
Drug (Generic)	**2020-2021 List Price Increase**	**Additional Spending Due to Price Increase (Total Population; Per-patient§)**
Darzalex (Daratumumab)	3.67%	$19.4 million; $481
Tyvaso (Tresprostinil)	7.38%	$18.2 million; $2,120

WAC: wholesale acquisition cost

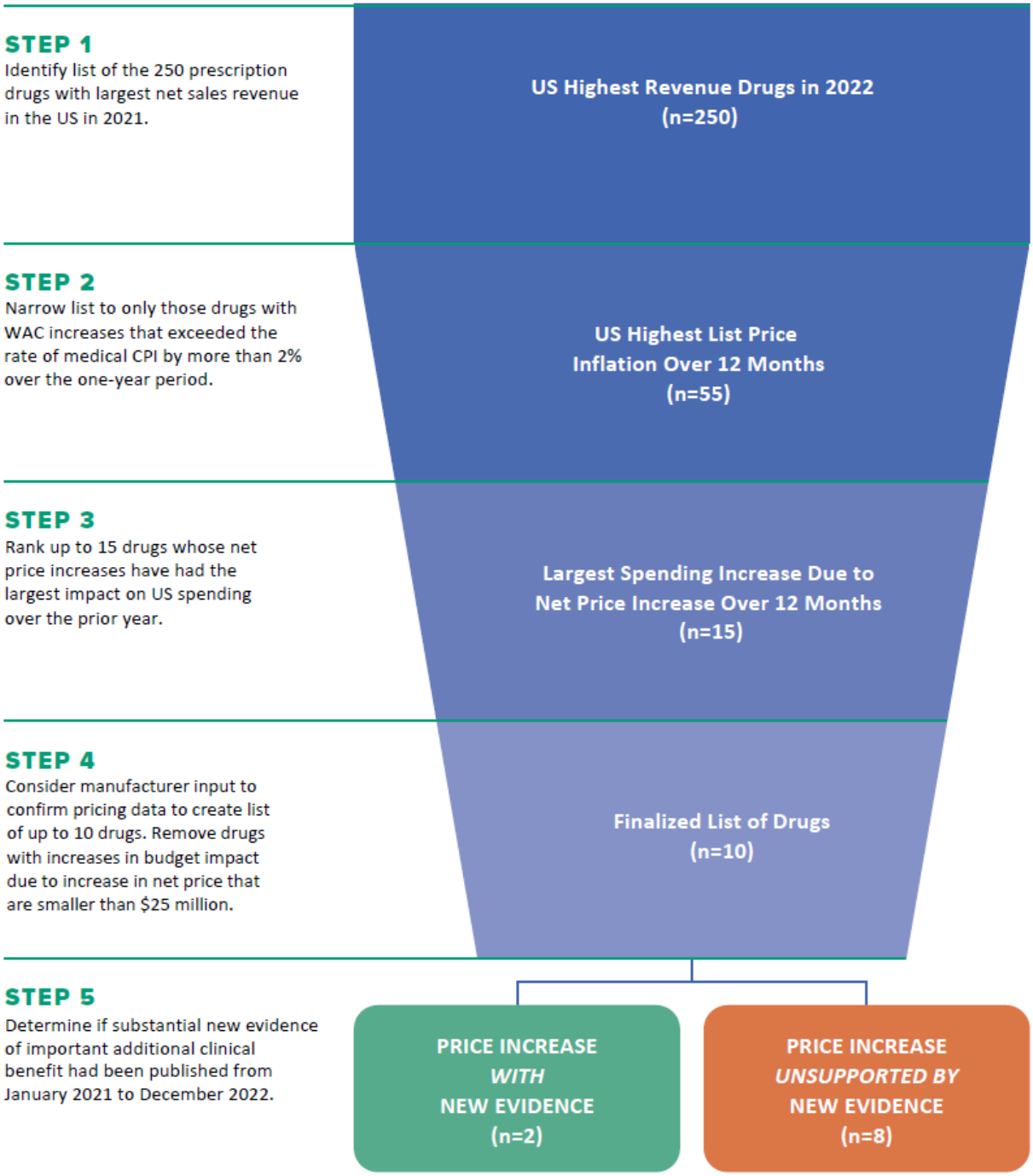
*Year-over-year percentage changes were estimated by averaging over the four quarterly changes in price (i.e., Q1 2021 to Q1 2022; Q2 2021 to Q2 2022; Q3 2021 to Q3 2022 and; Q4 2021 to Q4 2022).

†This is not a determination that the new evidence necessarily justified these price increases.

§Annual increase per-patient costs due to 20% coinsurance; for patients without supplemental insurance, this annual increase is out-of-pocket expense.

Figure ES1 on the following page shows the flow and process by which we selected the drugs for review.

Figure ES1. Drug Selection Process



1. Introduction

The price of many existing drugs, both brand and generic, can increase substantially over time, and questions are frequently raised regarding whether these price increases are justified. State policymakers have been particularly active in seeking measures to address this issue.[1-3]

In 2019, the Institute for Clinical and Economic Review (ICER) published its first Unsupported Price Increase (UPI) report after we organized a multi-stakeholder advisory group to provide input into the design of an approach for such reports. The advisory group is comprised of representatives from patient groups, drugmakers, and insurers representing Medicaid and the private market.

The annual UPI report may evaluate up to 13 drugs that have experienced substantial price increases. As described in later sections, this year's UPI report evaluated changes in the evidence base for 13 drugs and assessed whether there was potential evidentiary support for price increases. The first report looked back at two years of price increases and three years of new evidence, while subsequent reports have looked back at the price increase in the prior year and two years of new evidence.

ICER again worked with the advisory group to develop a revised UPI protocol for the reports. This year the protocol was changed to clarify that, in the unusual circumstance when multiple smaller indications of a drug, when combined, exceed 10% of overall utilization, and where every one of the indications individually has moderate- or high-quality evidence of a substantial new benefit compared with what was previously believed, ICER will consider this to be a price increase with new evidence.

It is important to note that ICER does not currently have the capacity to perform full economic analyses on the therapies evaluated in this report, nor would the time needed to develop full ICER reports (at least eight months) provide information in a useful timeframe for the public and policymakers. Therefore, this UPI report is not intended to determine whether a price increase for a drug is fully justified by new clinical evidence or meets an ICER health-benefit price benchmark. Instead, the analyses focused on whether substantial new evidence existed that *could* justify a price increase. By identifying whether there is, or is not, new evidence of improved safety or effectiveness for drugs with substantial price increases, we hope to take an important first step in providing the public and policymakers with information they can use to advance the public debate on drug price increases.

2. Selection of Drugs to Review

The goal of the drug selection process was to identify the top 10 drugs whose estimated net price increases over a one-year period would have caused the greatest increase in drug spending in the US. In addition, ICER examined three additional therapies that are heavily covered within the Medicare Part B program. A detailed description of the entire UPI Protocol is available separately.

ICER obtained a list of the 250 drugs with the largest net sales revenue in the US in 2022. This information came from SSR Health, LLC, an independent investment research firm. For each drug, we then determined the average WAC price changes over a one-year period. For this UPI Report, we looked at the average price in 2022 compared with the average price in 2021.

Table 2.1. List of Top 250 Drugs with the Highest Net Sales Revenue (in Millions) in the US in 2022

Drug Name	Revenue†	Δ WAC‡
Ranking†: 1-50		
Humira	**18,619**	**7.11%**
Keytruda	12,685	4.03%
Paxlovid	10,514	i
Comirnaty	**8,774**	**117.83%**
Biktarvy	8,510	5.49%
Revlimid	8,359	4.50%
Eliquis	7,786	6.00%
Dupixent	6,635	5.26%
Stelara	6,386	5.38%
Eylea	6,265	0.00%
Trulicity	5,689	5.00%
Ozempic	5,454	4.92%
Trikafta	4,905	4.90%
Opdivo	4,812	3.81%
Ocrevus	4,697	5.41%
Skyrizi	**4,484**	**7.12%**
Spikevax	4,405	-36.23%
Darzalex	**4,210**	**6.80%**
Enbrel	**4,044**	**8.75%**
Prevnar family	**4,031**	**6.92%**
Entyvio	**3,559**	**7.01%**
Jardiance	3,486	4.01%
Imbruvica	**3,426**	**7.25%**
Ibrance	**3,369**	**6.92%**
Cosentyx	**2,770**	**7.96%**
Invega Sustenna / Trinza	**2,714**	**6.21%**
Orencia	2,638	4.71%
Vyvanse	2,536	5.01%
Xtandi	2,494	5.78%
Xarelto	2,473	4.93%
Prolia	**2,465**	**7.64%**
Pomalyst	2,438	4.52%
Shingrix	2,429	5.89%
Hemlibra	2,424	2.50%
Jakafi	**2,409**	**8.33%**
Entresto	**2,354**	**7.96%**
Xolair	2,309	4.56%
Botox	2,255	2.71%
Soliris	2,179	0.00%
Tecentriq	2,067	4.00%
Gardasil / 9	2,065	5.62%
Vraylar	2,037	3.37%
Bamlanivimab	**2,009**	**1882.21 %**
Tagrisso	2,008	2.36%
Genvoya	1,984	5.52%
Tepezza	1,966	2.38%
Otezla	**1,886**	**10.45%**
Tremfya	1,844	5.40%
Rinvoq	1,794	7.10%
Fluzone	1,755	i
Ranking†: 51-100		
Taltz	1,725	5.02%
ProQuad / M-M-R II / Varivax	1,724	5.26%
Xifaxan	**1,693**	**6.48%**
Calquence	1,657	2.62%
Verzenio	1,653	5.53%
Descovy	1,631	5.52%
Latuda	1,630	5.28%
Perjeta	**1,605**	**6.08%**
Veklury	1,573	0.04%
Imfinzi	1,552	2.29%
Trelegy Ellipta	1,543	3.03%
Molnupiravir	1,523	i
Sprycel	1,497	4.50%
Triumeq	1,496	4.97%
Aubagio	1,493	5.72%
Xgeva	**1,480**	**7.53%**
Cimzia	1,448	5.91%
Ingrezza	1,428	5.51%
Remicade	1,417	0.01%
Rituxan	1,379	0.00%
Cabometyx	**1,379**	**7.50%**
Yervoy	1,304	3.81%
Creon	**1,278**	**6.06%**
Actemra	1,257	3.22%
Januvia	1,248	4.95%
Vyndaqel/Vyndamax	1,245	5.58%
Lynparza	1,227	3.09%
Lenvima	1,187	5.58%
Simponi / Aria	1,166	1.80%
Benlysta	1,165	5.23%
Activase / TNKase	1,165	1.33%
Rexulti	**1,161**	**6.93%**
Gilenya	1,153	5.93%
Ultomiris	1,136	0.00%
Opsumit	1,132	5.78%
Rybelsus	**1,132**	**6.86%**
Xeljanz	1,129	5.57%
Tysabri	1,123	5.27%
Uptravi	**1,104**	**6.78%**
Nucala	1,085	4.31%
Promacta	**1,083**	**7.93%**
Farxiga / Xigduo	1,070	3.04%
Sotrovimab	1,069	0.29%
Evusheld	1,068	i
Lucentis	1,060	0.27%
Odefsey	1,058	5.52%
Xyrem	**1,020**	**8.17%**
Tivicay	1,011	4.98%
Venclexta	1,009	5.81%
Linzess	1,003	4.81%
Ranking†: 101-150		
Jynarque	988	i
Erleada	968	5.39%
Austedo	**962**	**7.87%**
Neulasta	959	1.86%
Xywav	**958**	**8.19%**
Dovato	950	4.97%
Bridion	922	5.00%
Kesimpta	**921**	**7.46%**
Victoza	907	4.98%
Humalog / Mix	905	0.01%
Fasenra	905	3.09%
Tasigna	**877**	**6.95%**
Tyvaso	873	4.90%
Novolog / Mix	871	-0.03%
Wegovy	865	-0.01%
Symtuza	863	5.57%
Kadcyla	859	5.59%
Enhertu	850	4.33%
Kyprolis	**850**	**7.65%**
Lantus	800	0.02%
Sandostatin / LAR	800	0.00%
Adcetris	**797**	**8.69%**
Takhzyro	797	3.00%
Strensiq	770	0.00%
Symbicort	758	1.90%
Vimpat	756	5.98%
Mavyret	755	-0.01%
Abilify Maintena	**754**	**6.85%**
Nurtec ODT	750	2.97%
Yescarta	747	i
Brilinta	744	4.05%
Myrbetriq	734	2.94%
Humulin / Mix	730	0.00%
Lexiscan	720	2.05%
Krystexxa	716	5.99%
Trintellix	690	5.01%
Ubrelvy	680	4.82%
Tafinlar / Mekinist	**678**	**6.39%**
Avastin	665	0.00%
Epidiolex	**663**	**8.45%**
Avonex	649	3.69%
Fluarix / FluLaval	645	i
Nplate	**641**	**7.61%**
Prezista / Prezcobix	**631**	**6.58%**
Restasis	621	4.79%
Inlyta	**618**	**6.90%**
Breo Ellipta	**618**	**3.10%**
Saxenda	612	0.15%
Repatha	**608**	**7.59%**
Juluca	606	4.97%
Ranking†: 151 - 200		
Mvasi	602	1.86%
Spinraza	600	i
Reblozyl	591	3.04%
Abraxane	580	4.50%
Implanon / Nexplanon	573	5.26%
Ilaris	570	1.81%
Rebif	561	4.01%
Gattex	559	-94.90%
Menactra	550	4.74%
Alimta	544	5.07%
Novoseven / RT	541	3.44%
Exparel	537	4.07%
Vabysmo	537	i

Drug Name	Revenue†	Δ WAC‡
Evenity	**533**	**7.56%**
Trodelvy	524	5.02%
Vumerity	521	3.26%
Aranesp	521	0.00%
Nuplazid	**517**	**12.77%**
Exondys 51	512	0.00%
RotaTeq	509	3.18%
Epogen	506	0.00%
Erbitux	500	5.08%
Herceptin	500	0.00%
Fabrazyme	495	4.78%
Evrysdi	492	3.56%
Esbriet	479	3.00%
Eloctate	474	3.49%
Alecensa	474	4.80%
Kisqali	**472**	**6.98%**
Basaglar	471	0.00%
Emgality	463	4.01%
Padcev	**451**	**7.15%**
Acthar	448	3.72%
Boostrix	443	2.91%
Advate	441	2.94%
Xiaflex	**439**	**7.89%**
Wakix	438	5.01%
Flovent	437	2.91%
Zolgensma	434	-0.14%
Ninlaro	431	5.13%
Vemlidy	429	5.51%
Alprolix	427	3.31%
Premarin family	419	3.47%

Drug Name	Revenue†	Δ WAC‡
Tecfidera	418	1.44%
Zirabev	413	0.00%
Sublocade	409	5.01%
Bexsero	407	5.02%
Infanrix / Pediarix	404	0.51%
Ruxience	403	0.00%
Briviact	**399**	**6.91%**
Ranking†: 201-250		
Aimovig	**398**	**7.55%**
Injectafer	397	5.27%
Vectibix	**396**	**7.60%**
Velcade	387	0.00%
Tresiba	387	0.00%
Tradjenta	387	4.01%
Pulmozyme	386	3.61%
Copaxone	386	-0.01%
Vivitrol	380	5.01%
Advair	379	-1.73%
Remodulin	378	0.00%
Vyvgart	378	i
Bosulif	375	5.56%
Libtayo	375	2.62%
Epclusa	368	-0.02%
Forteo	367	5.00%
Mounjaro	367	i
Multaq	**364**	**6.75%**
Gazyva	361	5.96%
Vascepa	360	2.98%
Cabenuva	357	3.81%

Drug Name	Revenue†	Δ WAC‡
Janumet / XR	355	4.95%
Kalydeco	353	4.90%
Tukysa	**353**	**6.21%**
Venofer	353	2.91%
Cyramza	351	5.07%
Pneumovax 23	346	3.66%
Blincyto	**336**	**7.58%**
Myozyme / Lumizyme	335	4.48%
Lamictal / XR	**327**	**6.99%**
Orkambi	326	4.90%
Ravicti	326	0.42%
Orenitram ER	325	4.90%
Inomax	323	i
Phesgo	318	0.00%
Retacrit	311	0.01%
Aristada	302	3.07%
Abecma	297	i
Toujeo	297	0.05%
Lonsurf	294	4.87%
Suboxone Film	294	0.00%
Menveo	293	3.30%
Zejula	**290**	**7.00%**
Jevtana	290	5.50%
Inflectra	289	0.00%
Adacel	288	4.43%
Ocaliva	286	5.85%
Anoro Ellipta	285	2.55%
Synjardy / XR	285	4.01%
Iclusig	**284**	**7.06%**

Bolding indicates the 55 drugs subset from the greater 250 that had a WAC price increase greater than medical CPI + 2%
WAC: wholesale acquisition cost
Insufficient WAC change information is denoted by i
*No WAC change percentage is given when WAC data required to calculate WAC percentage change were not available in one or more quarters. Had the WAC percentage increases been larger than medical CPI + 2%, the drugs where WAC was unavailable still would not have been included in the list of drugs to be assessed.
†Net sales revenue in 2020, in millions.
‡Four quarter WAC change.
§Provided by manufacturer.

We then determined which of those drugs had a WAC price increase over the one-year period that exceeded the rate of medical CPI + 2%. This was calculated as the difference between the average medical CPI using unadjusted rates, which was 4.05% for 2022 relative to 2021. The medical CPI is one of eight major components of the CPI recorded and reported by the US Bureau of Labor Statistics.[5] Medical CPI comprises medical care services (professional services, hospital and related services, and health insurance) and medical care commodities (medical drugs, equipment, and supplies).[6] Drugs whose WAC price percentage increases had not exceeded the rate of medical CPI + 2% (6.05%) were removed from further evaluation. Our intent in choosing the overall medical CPI and not its subcomponents was to reflect inflation in drug prices relative to inflation in the overall price of medical care.

Among those 55 drugs with a WAC price increase greater than the medical CPI + 2%, we determined *net* price changes over the one-year period. WAC and net price change per unit over the one-year period were adjusted for percentage change in price across different dosing strengths for any drug, if applicable, considering the relative sales volume of the various dosing strengths. Net price information was obtained from SSR Health. Drugs for which pricing information was deemed unreliable (e.g., because the net price was higher than WAC price in at least one of the eight quarters in which data were captured) were excluded from this review.

Table 2.2 shows the top 15 drugs ranked by the effect of net price increases on US spending per SSR Health data. Manufacturers were given the opportunity to correct these figures early in the process; however, the data presented in Table 2.2 represent spending-determined rankings prior to manufacturer feedback. After the receipt of manufacturer feedback, we arrived at the top 10 drugs derived from SSR Health based on their corrected increase in drug spending due to net price change.

Table 2.2. Top 15 Drugs with WAC Percentage Change Greater than Medical Care CPI* + 2% Ranked by Increase in Spending Due to Net Price Change, Prior to Manufacturer Feedback

Drug Name	Rank
Humira	1
Ibrance	2
Darzalex	3
Jakafi	4
Prolia	5
Perjeta	6
Xywav	7
Xyrem	8
Xifaxan	9
Xgeva	10
Adcetris	11
Entresto	12
Cabometyx	13
Inlyta	14
Iclusig	15

*Medical care CPI was 4.05% in 2021.

Beyond the 10 drugs identified, an additional three were highlighted based on their high estimates of increased spending due to net price increases. These three Part B drugs were identified based on changes in Centers for Medicare and Medicaid Services (CMS) average spending per dosage unit and were ranked based on changes in total population-based increased spending due to increases in unit prices. Because of the timing of information from CMS, the three additional therapies identified from the Medicare Part B database used the average price in 2021 compared with the average price in 2020 and so overlapped with the time from the prior UPI report. Unique to the three Part B drugs is the increase in spending at the patient level, given 20% coinsurance based on increases in unit prices. For example, for Nplate, a patient or their optional supplemental insurer

would be responsible for paying an average of $684 more per year based on the increase in unit price from 2020 to 2021. As with the main top 10 drugs, manufacturers also had a chance to review and comment on those prices for the three Part B drugs.

Table 2.3 shows the 13 drugs that were chosen for assessment. This includes 10 drugs that were selected from Table 2.2 after manufacturer review and proposed revisions had occurred. Thus, rankings and estimates of increases in drug spending were subject to change between Table 2.2 and Table 2.3.

Table 2.3. Drugs Selected for Assessment

Drug (Generic)	2021 to 2022 Percentage Change*		Increase in Drug Spending Due to Net Price Change (in Millions)
	WAC	Net Price	
Drugs with Price Increases Unsupported by New Clinical Evidence			
Humira (Adalimumab)	7.11%	1.95%	$386
Darzalex (Daratumumab)	6.80%	6.18%	$248
Ibrance (Palbociclib)	6.92%	4.45%	$151
Prolia (Denosumab)	7.64%	5.99%	$140
Xifaxan (Rifaxamin)	6.48%	5.83%	$98
Xgeva (Denosumab)	7.53%	7.23%	$97
Perjeta (Pertuzumab)	6.08%	6.07%	$91
Adcetris (Brentuximab Vedotin)	8.69%	8.92%	$63
Drugs with Price Increases with New Clinical Evidence†			
Jakafi (Ruxolitinib)	8.33%	5.16%	$118
Entresto (Sacubitril/Valsartan)	7.96%	2.56%	$57
Part B Drugs with Price Increases Unsupported by New Clinical Evidence			
Drug (Generic)	**2020-2021 List Price Increase**	**Additional Spending Due to Price Increase (Total Population; Per-patient§)**	
Nplate (Romiplostim)	6.81%	$17 million; $684	
Part B Drugs with Price Increases with New Clinical Evidence†			
Drug (Generic)	**2020-2021 List Price Increase**	**Additional Spending Due to Price Increase (Total Population, Per-patient§)**	
Darzalex (Daratumumab)	3.67%	$19.4 million; $481	
Tyvaso (Tresprostinil)	7.38%	$18.2 million; $2,120	

WAC: wholesale acquisition cost

*Year-over-year percentage changes were estimated by averaging over the four quarterly changes in price (i.e., Q1 2021 to Q1 2022; Q2 2021 to Q2 2022; Q3 2021 to Q3 2022 and; Q4 2021 to Q4 2022).

†This is not a determination that the new evidence necessarily justified these price increases.

§Annual increase per-patient costs due to 20% coinsurance; for patients without supplemental insurance, this annual increase is out-of-pocket expenses.

In this year's UPI Report, two drugs appear twice. Darzalex (daratumumab) appears as one of eight drugs on the main list judged as having a price increase **unsupported** by new clinical evidence and also as one of two drugs on the separate Medicare list judged as having a price increase **with** new clinical evidence. As discussed above, the time period for price increases for the main list was 2021 to 2022 and for the Medicare list was 2020 to 2021. The evidence review looks back two years from

the period of the price increase and thus the body of evidence was different in judging these two Darzalex price increases. Denosumab appears separately on the main list under its two brand names, Prolia and Xgeva. These products have different indications, dosing regimens, and pricing, and each individually had price increases that met criteria to appear on the UPI list. While the bodies of evidence differed for these two products, the price increases were both found to be unsupported by new clinical evidence.

3. Assessments (Main List)

3.1 Humira® (Adalimumab, AbbVie)

Introduction

Humira® (adalimumab, AbbVie) is a humanized monoclonal antibody that binds specifically to tumor necrosis factor (TNF).[7] It was approved by the Food and Drug Administration (FDA) in 2002, and is indicated for the treatment of nine different chronic diseases: rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, adult and pediatric Crohn's disease, adult and pediatric ulcerative colitis, plaque psoriasis, adult and adolescent hidradenitis suppurativa, and adult and pediatric noninfectious uveitis.

Based on clinical input, the indications that account for greater than 10% of adalimumab's use include:

- Rheumatoid arthritis
- Psoriatic arthritis
- Adult Crohn's disease
- Adult ulcerative colitis
- Plaque psoriasis.

Price Increase

Over the 12 months (four quarters) for which price changes were assessed, the WAC for adalimumab increased by approximately 7.11%, while its estimated net price increased by 1.95%. This net price change over the assessed four quarters resulted in an estimated increase in drug spending of $386 million. All pricing information was obtained from SSR Health, LLC.

Review of Clinical Evidence

We reviewed the safety and clinical effectiveness information provided in the FDA label as well as related published literature to assess the baseline evidence on adalimumab as of January 2021. Following that, we conducted an independent systematic literature review, limited to RCTs, over the 24 months review timeframe (January 2021 – December 2022) (see Appendix Table M1). In addition, we reviewed the RCT and non-RCT information AbbVie submitted to us to consider as new clinical information (six references [one conference presentation and five published manuscripts]). However, none of the identified or submitted articles met our criteria of new moderate to high-quality evidence on the benefits and/or harms of adalimumab within the indications that account for greater than 10% of use (Appendix Table A1). The six references submitted by the manufacturer

were excluded because they did not meet our UPI review criteria. The primary reasons for excluding these studies are provided in Table 3.1 (Appendix A provides additional information on each study).

Table 3.1. Studies Not Meeting UPI Review Criteria

Reason	Number of References
Study published outside of the timeframe of our review	1
Intervention/comparison not relevant to scope	5

For simplicity, we provide a single reason for exclusion of each study, although there may be multiple reasons why a study was excluded.

Study Not Meeting UPI Criteria

Fendrick 2021 was a retrospective matched-cohort study that evaluated the long-term effects of participation in a patient support program (PSP) on medication-taking behavior and hospitalizations beyond 12 months of treatment.[8] The study included 2,268 commercially insured patients who initiated adalimumab and had data for at least six months prior and at least 12 months post initial adalimumab insurance claim. Two cohorts, PSP (n=1,134) and non-PSP (n=1,134) were matched based on factors such as disease indication, pharmacy type, and baseline comorbidities and followed for up to 36 months. Medication-taking behavior, including adherence and persistence, and hospital visits were assessed. The PSP cohort reported higher medication adherence (39.4% v. 35.1%; p=0.02) and persistence (27% v. 19%; p<0.0001) at month 36 compared to the non-PSP cohort. The median time to hospital visit for patients in the PSP cohort was 11.8 months longer than the non-PSP cohort. Similarly, there was a lower rate of hospital visits in the PSP cohort at month 36 (55% v. 65%; p<0.01).

Reason(s) for Not Meeting UPI Criteria

Fendrick 2021 is a retrospective study that evaluated the impact of patient support programs on patient-important outcomes, with adalimumab in both comparison arms. It provides evidence on how a patient support program can improve patient outcomes but does not provide evidence for a new net benefit of adalimumab.

Conclusion

After careful review of the evidence submitted by the manufacturer, we conclude that adalimumab (Humira®) had a price increase *unsupported* by new clinical evidence.

3.2 Darzalex® (Daratumumab, Janssen)

Introduction

Darzalex® (daratumumab, Janssen) is an anti-CD38 monoclonal antibody that first received FDA approval in 2015.[9] It is indicated for the treatment of adult patients with multiple myeloma as both a monotherapy and in combination with other agents.

Price Increase

Over the 12 months (four quarters) for which price changes were assessed, the WAC for daratumumab increased by approximately 6.8%, while its estimated net price increased by 6.18%. This net price change over the assessed four quarters resulted in an estimated increase in drug spending of $248 million. All pricing information was obtained from SSR Health, LLC.

Review of Clinical Evidence

We reviewed the safety and clinical effectiveness information provided in the FDA label as well as related published literature to assess the baseline evidence on daratumumab as of January 2021. Following that, we conducted an independent systematic literature review, limited to RCTs, over the 24 months review timeframe (January 2021 – December 2022)(see Appendix Table M1). Our literature search identified 22 articles, none of which met our inclusion criteria of new and potentially moderate- to high-quality evidence on the benefits and/or harms of daratumumab. Janssen did not submit any additional references to be considered for our review.

Conclusion

After careful review of the evidence, we conclude that daratumumab (Darzalex®) had a price increase *unsupported* by new clinical evidence. The time period of the evidence review for the main list assessment (2021-2022) is different from the time period for the Medicare Part B assessment (2020-2021) described in Section 4.

3.3 Ibrance® (Palbociclib, Pfizer)

Introduction

Ibrance® (palbociclib, Pfizer) is a kinase inhibitor approved by the FDA in 2015.[10] It is indicated for the treatment of hormone receptor-positive, human epidermal growth factor receptor 2-negative (HR+/HER2-) advanced or metastatic breast cancer in adults. It is used in combination with either an aromatase inhibitor as an initial endocrine based therapy or with fulvestrant in those with disease progression after endocrine therapy.

Price Increase

Over the 12 months (four quarters) for which price changes were assessed, the WAC for palbociclib increased by approximately 6.92%, while its estimated net price increased by 4.45%. This net price change over the assessed four quarters resulted in an estimated increase in drug spending of $151 million. Estimates of percent change in net price and budget impact due to net price changes in 2022 were provided by the manufacturer.

Review of Clinical Evidence

We reviewed the safety and clinical effectiveness information provided in the FDA label as well as related published literature to assess the baseline evidence on palbociclib as of January 2021. Following that, we conducted an independent systematic literature review, limited to RCTs, over the 24 months review timeframe (January 2021 – December 2022) (see Appendix Table M1). In addition, we reviewed the RCT and non-RCT information Pfizer submitted to us to consider as new clinical information (16 references [five conference presentation and 11 published manuscripts]). However, none of the identified or submitted articles met our criteria of new moderate to high-quality evidence on the benefits and/or harms of palbociclib (Appendix Table C1). Of the 16 references submitted by the manufacturer, four articles were excluded because they did not meet our UPI review criteria. The primary reasons for excluding these studies are provided in Table 3.2. Of the remaining 12 articles, nine presented previously known information about palbociclib, while the remaining three studies were considered low-quality evidence (see Table 3.3). As an example, we highlighted a submitted article (DeMichele et al. 2021) that we classified as low-quality evidence.[11]

Table 3.2. Studies Not Meeting UPI Review Criteria

Reason	Number of References
Study published outside of the timeframe of our review	3
Study population outside approved label indication	1

For simplicity, we provide a single reason for exclusion of each study, although there may be multiple reasons why a study was excluded.

Table 3.3. Studies Not Meeting Criteria for New Moderate to High-Quality Evidence

Reasons	Number of References
Low-quality evidence	3
Previously known information about palbociclib related to efficacy	8
Previously known information about palbociclib related to safety	1

Study Not Meeting New Moderate to High-Quality Evidence

DeMichele et al. 2021 was a retrospective observational study that evaluated the effectiveness of palbociclib plus letrozole compared to letrozole alone. Electronic health records of 1430 patients with hormone-receptor (HR+), human epidermal growth factor receptor-negative (HER2-) metastatic breast cancer who initiated either treatment option between 2015 and 2019 and had ≥3 months of follow-up were included in the analysis. Progression-free survival and overall survival were the key outcomes evaluated. The analysis showed a significantly longer median progression-free survival among people on palbociclib plus letrozole compared to letrozole alone (hazard ratio: 0.58; 95%CI: 0.49, 0.69). Similarly, there was a statistically significant improvement in overall survival in the palbociclib plus letrozole group compared to the letrozole group (Median OS: palbociclib group – not reached; letrozole group - 43.1 months; HR: 0.66, 95% CI: 0.53-0.82). The 2-year overall survival rate was 78.3% in the palbociclib plus letrozole group versus 68.0% in the letrozole group. Similar results were observed for both outcomes among subgroups of interest (e.g., age, race, symptom severity).

Reason(s) for Not Meeting New Moderate to High-Quality Evidence

De Michele 2021 is a well-performed retrospective observational analysis conducted to evaluate the overall survival of patients treated with palbociclib. However, using GRADE criteria, this evidence is considered low quality in the absence of specific criteria that would increase the evidence rating. Such criteria are not found in this case. Under the UPI Protocol we do not assess the magnitude of benefit in the absence of moderate or high-quality evidence.

Conclusion

After careful review of the evidence, we conclude that palbociclib (Ibrance®) had a price increase *unsupported* by new clinical evidence.

3.4 Prolia® (Denosumab, Amgen)

Introduction

Prolia® (denosumab, Amgen), a monoclonal antibody used to manage osteoporosis in patients at high risk of fractures, was first approved by the FDA in 2010.[12] It is specifically indicated for the treatment of osteoporosis in the following patients: postmenopausal women at high risk for fracture, men at high risk for fracture, men and women with glucocorticoid-induced osteoporosis at high risk for fracture, men undergoing androgen deprivation therapy for nonmetastatic prostate cancer at high risk for fracture, and women receiving adjuvant aromatase inhibitor therapy for breast cancer at high risk for fracture. Based on information provided by the manufacturer, all indications, other than the treatment of osteoporosis in men, account for >10% of use.

Price Increase

Over the 12 months (four quarters) for which price changes were assessed, the WAC for denosumab increased by approximately 7.64%, while its estimated net price increased by 5.99%. This net price change over the assessed four quarters resulted in an estimated increase in drug spending of $140 million. All pricing information was obtained from SSR Health, LLC.

Review of Clinical Evidence

We reviewed the safety and clinical effectiveness information provided in the FDA label as well as related published literature to assess the baseline evidence on denosumab as of January 2021. Following that, we conducted an independent systematic literature review, limited to RCTs, over the 24 months review timeframe (January 2021 – December 2022) (see Appendix Table M1). In addition, we reviewed the RCT and non-RCT information Amgen submitted to us to consider as new clinical information (13 references [three conference presentation and ten published manuscripts]). However, none of the identified or submitted articles met our criteria of new moderate to high-quality evidence on the benefits and/or harms of denosumab (see Appendix Table D1). Of the 13 references submitted by the manufacturer, four articles were excluded because they did not meet our UPI review criteria (see Table 3.4). Of the remaining nine articles, two were considered low quality and seven were considered previously known information about denosumab (See Table 3.5). As an example, we highlighted one submitted article (Kim et al. 2022) we classified as low-quality evidence.[13]

Table 3.4. Studies Not Meeting UPI Review Criteria

Reason	Number of References
Study published outside of the timeframe of our review	3
Intervention/comparison not relevant to scope	1

For simplicity, we provide a single reason for exclusion of each study, although there may be multiple reasons why a study was excluded.

Table 3.5. Studies Not Meeting Criteria for New Moderate to High-Quality Evidence

Reasons	Number of References
Low-quality evidence	2
Previously known information about denosumab related to efficacy	7

Study Not Meeting Criteria for New Moderate- to High-Quality Evidence

Kim et al. 2022 was real-world analysis evaluating the comparative effectiveness of denosumab versus alendronate in reducing fracture risk.[13] Commercial and Medicare Advantage claims data were used to identify post-menopausal women who initiated either denosumab (n=13,871) or alendronate (n=8,747) from 2012 to 2019. The analysis showed no difference in fracture outcomes between denosumab and alendronate during the whole study period (2012-2019). However, in the more recent cohort (i.e., patients initiating treatment in 2015 or later), denosumab had greater reductions in hip fractures (risk ratio: 0.52; 95%CI: 0.28, 0.77) and non-vertebral fractures (risk ratio: 0.75; 95%CI: 0.5, 0.99) compared to patients treated with alendronate.

Reason(s) for Not Meeting Criteria for New Moderate- to High-Quality Evidence

The results from this study are derived from an abstract presented at the American College of Rheumatology Convergence; therefore detailed methodology and complete results are not available. However, based on the limited information available, evidence from Kim et al. 2022 is considered low quality in the absence of specific criteria that would increase the quality of evidence. Under the UPI Protocol, we do not assess the magnitude of benefit in the absence of moderate or high-quality evidence

Conclusion

After careful review of the evidence, we conclude that denosumab (Prolia®) had a price increase *unsupported* by new clinical evidence.

3.5 Jakafi® (Ruxolitinib, Incyte)

Introduction

Jakafi® (ruxolitinib, Incyte) is a kinase inhibitor approved by the FDA in 2011.[14] It is indicated for myelofibrosis (intermediate or high risk), polycythemia vera (in adults who are intolerant or have an inadequate response to hydroxyurea), steroid-refractory acute graft versus host disease (in patients aged 12 and older), and was most recently approved in September 2021 for chronic graft-versus-host disease post failure of one to two lines of systemic therapy (in patients aged 12 and older). Based on the information provided by the manufacturer, all indications account for greater than 10% of use.

Price Increase

Over the 12 months (four quarters) for which price changes were assessed, the WAC for ruxolitinib increased by approximately 8.33%, while its estimated net price increased by 5.16%. This net price change over the assessed four quarters resulted in an estimated increase in drug spending of $118 million. Estimates of percent change in net price and budget impact due to net price changes in 2022 were provided by the manufacturer.

Review of Clinical Evidence

We reviewed the safety and clinical effectiveness information provided in the FDA label as well as related published literature to assess the baseline evidence on ruxolitinib as of January 2021. Following that, we conducted an independent systematic literature review, limited to RCTs, over the 24 months review timeframe (January 2021 – December 2022) (see Appendix Table M1). In addition, we reviewed the RCT and non-RCT information Incyte submitted to us to consider as new clinical information (ten references [six conference presentation and four published manuscripts]). We identified two references (REACH-3[15] and MAJIC-PV[16]) that met our criteria of new and potentially moderate- to high-quality evidence on the benefits and/or harms of ruxolitinib. Additional details are provided below (Table 3.8). Of the remaining eight references, five were excluded because the study population was outside the approved label indications and three were considered low quality (See Tables 3.6 and 3.7).

Table 3.6. Studies Not Meeting UPI Review Criteria

Reason	Number of References
Study population outside approved label indication	5

For simplicity, we provide a single reason for exclusion of each study, although there may be multiple reasons why a study was excluded.

Table 3.7. Studies Not Meeting Criteria for New Moderate to High-Quality Evidence

Reasons	Number of References
Low-quality evidence	3

Table 3.8. Summary of New Evidence

Baseline Evidence (Before January 2021)	New Evidence
Ruxolitinib was approved for use in individuals with polycythemia vera in 2014 based on the RESPONSE trial.[17]	The **MAJIC-PV** study was an RCT that evaluated the efficacy and safety of ruxolitinib compared to the best available therapy in patients with polycythemia vera who are resistant or intolerant to hydroxycarbamide.[16] This study confirmed the benefit of ruxolitinib for hematologic control and symptom responses, but also extended the evidence base by demonstrating that ruxolitinib improves thrombosis-free survival, event-free survival and molecular response.
Prior to September 2021, ruxolitinib was not indicated for individuals with chronic graft-vs.-host disease.	The **REACH-3** study was an RCT that evaluated the efficacy and safety of ruxolitinib compared to the investigator's choice of 10 commonly used options (considered best available care) in patients with moderate or severe glucocorticoid-refractory of dependent chronic graft-vs.-host disease.[15] Based on the evidence from the REACH-3 trial, the FDA granted approval for ruxolitinib for the treatment of chronic graft-vs.-host disease after failure of one or two lines of systemic therapy in individuals 12 years and older.

FDA: Food and Drug Administration, RCT: randomized controlled trial

New Evidence

The **MAJIC-PV** study was a Phase II open-label RCT that enrolled patients with polycythemia vera who were either resistant or intolerant to hydroxycarbamide. Patients were randomized to receive either oral ruxolitinib (n=70) or best available therapy (n=57).[16,18] Complete response was observed in more patients receiving ruxolitinib compared the best available therapy (odds ratio: 2.12 [90% CI: 1.08, 1.33]; p<0.001) and ruxolitinib maintained better symptom responses up to 52 months. Thromboembolic-event free survival (hazard ratio: 0.56 [95% CI: 0.32, 1.00]; p=0.05) and event-free survival (composite of major thrombosis, major hemorrhage, transformation, or death; hazard

ratio: 0.58 [95%CI: 0.35, 0.94]; p=0.03) were significantly improved with the use of ruxolitinib. Similar trend was observed in PFS (transformation into myelofibrosis, myelodysplastic syndrome, or AML, or death from any cause), although statistical significance was not achieved. There was no statistically significant difference in overall survival. At the last available time point, 56% of patients who received ruxolitinib achieved greater than a 50% reduction in $JAK2^{V617F}$ VAF compared to 25% receiving best available therapy. This reduction was associated with achieving complete response, improvements in survival, and clearance of MPN stem cells.

The **REACH-3** study was a Phase III open-label multicenter RCT that enrolled adolescent and adult patients 12 years and older with moderate-to-severe glucocorticoid-refractory or dependent graft-versus-host disease.[15] Patients were randomized to receive either oral ruxolitinib 10 mg twice daily (n=165) or the investigator's choice of 10 commonly used second-line treatments (n=164), stratified by disease severity. At week 24, the overall response rate was higher in the ruxolitinib arm compared with the control arm (49.7% vs. 25.6%; odds ratio: 2.99; P<0.001). Similarly, there was a longer median failure-free survival in the ruxolitinib arm (>18.6 months) than in the control arm (5.7 months) (hazard ratio: 0.37; P<0.001). However, overall survival was not mature at the data cutoff. Thrombocytopenia (15.2% in the ruxolitinib arm vs. 10.1% in the control arm) and anemia (12.7% in the ruxolitinib arm vs. 7.6% in the control arm) were the most common grade 3+ adverse events reported.

Rating of New Evidence (Quality and Magnitude):

Before **MAJIC-PV**, ruxolitinib was approved for polycythemia vera in adults who are intolerant or have an inadequate response to hydroxyurea study based on hematologic control and symptomatic improvement. However, MAJIC-PV provides new evidence that indicates ruxolitinib significantly improves thrombosis-free survival and event-free survival (major thrombosis, hemorrhage, transformation, and death) and reduces the malignant clone, which was an area of uncertainty. The trial was open-label, providing moderate-quality evidence of substantial benefit for ruxolitinib versus other commonly used therapies for patient-important outcomes in those with polycythemia vera who are intolerant or have an inadequate response to hydroxyurea.

REACH 3 trial was one of the two qualifying new moderate-to-high-quality evidence for ruxolitinib in the 2022 UPI report. Since our UPI protocol requires only one new moderate-to-high-quality evidence of substantial net benefit, this trial was accepted as new evidence for this year's review since it falls within the current evidence review time frame.

Rating from ICER's 2022 UPI Report: *Based on evidence from REACH-3, the FDA approved ruxolitinib for chronic graft-versus-host disease after failure of one or two lines of systemic therapy in individuals 12 years and older. The trial was open-label, providing moderate-quality evidence of a substantial benefit for ruxolitinib that was not previously known for patients 12 years and older with chronic graft-versus-host disease who have been failed by one or two lines of systemic therapy.*

We have no reason to alter this assessment of REACH-3.

Conclusion

After careful review of the evidence, we conclude that ruxolitinib (Jakafi®) had a price increase *with* new clinical evidence.

3.6 Xifaxan® (Rifaxamin, Bausch Health)

Introduction

Xifaxan® (rifaximin, Bausch Health) is a rifamycin antibacterial drug approved by the FDA in 2004.[19] It is indicated for treatment of traveler's diarrhea caused by noninvasive strains of Escherichia coli (E. coli) in adult and pediatric patients (age 12 years and older), reduction in risk of overt hepatic encephalopathy recurrence in adults, and was most recently approved in 2015 for the treatment of irritable bowel syndrome with diarrhea (IBS-D) in adults.

Based on the information provided by the manufacturer, the indications that account for greater than 10% of rifaximin's use include:

- Reduction in risk of overt hepatic encephalopathy recurrence
- Treatment of IBS-D.

Price Increase

Over the 12 months (four quarters) for which price changes were assessed, the WAC for rifaximin increased by approximately 6.48%, while its estimated net price increased by 5.83%. This net price change over the assessed four quarters resulted in an estimated increase in drug spending of $98 million. All pricing information was obtained from SSR Health.

Review of Clinical Evidence

We reviewed the safety and clinical effectiveness information provided in the FDA label as well as related published literature to assess the baseline evidence on rifaximin as of January 2021. Following that, we conducted an independent systematic literature review, limited to RCTs, over the 24 months review timeframe (January 2021 – December 2022) (see Appendix Table M1). Our literature search identified 19 articles, none of which met our inclusion criteria of new and potentially moderate- to high-quality evidence on the benefits and/or harms of rifaximin. Bausch Health did not submit any additional references to be considered for our review.

Conclusion

After careful review of the evidence, we conclude that rifaximin (Xifaxan®) had a price increase *unsupported* by new clinical evidence.

3.7 Xgeva® (Denosumab, Amgen)

Introduction

Xgeva® (denosumab, Amgen) is a RANK ligand (RANKL) injection originally approved by the FDA in 2010.[20] It is indicated for the prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors, treatment of giant cell tumor of the bone in adults and skeletally mature adolescents, and treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy. We did not receive input from the manufacturer on which indications account for greater than 10% of use; since it did not affect the conclusions of our review, we did not attempt to obtain additional information from clinical experts or payers on this issue.

Price Increase

Over the 12 months (four quarters) for which price changes were assessed, the WAC for denosumab increased by approximately 7.53%, while its estimated net price increased by 7.23%. This net price change over the assessed four quarters resulted in an estimated increase in drug spending of $97 million. All pricing information was obtained from SSR Health, LLC.

Review of Clinical Evidence

We reviewed the safety and clinical effectiveness information provided in the FDA label as well as related published literature to assess the baseline evidence on denosumab as of January 2021. Following that, we conducted an independent systematic literature review, limited to RCTs, over the 24 months review timeframe (January 2021 – December 2022) (see Appendix Table M1). Our literature search identified 47 articles, none of which met our inclusion criteria of new and potentially moderate- to high-quality evidence on the benefits and/or harms of denosumab. Amgen did not submit any additional references to be considered for our review.

Conclusion

After careful review of the evidence, we conclude that denosumab (Xgeva®) had a price increase *unsupported* by new clinical evidence.

3.8 Perjeta® (Pertuzumab, Genentech)

Introduction

Perjeta® (pertuzumab, Genentech) is a humanized monoclonal antibody approved by the FDA in 2012.[21] It is used in combination with trastuzumab and docetaxel for patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. Perjeta, in combination with trastuzumab and chemotherapy, is also approved as neoadjuvant treatment for HER2-positive, locally advanced, inflammatory, or early-stage breast cancer and adjuvant treatment for HER2-positive early breast cancer at high risk of recurrence. We did not receive input from the manufacturer on which indications account for greater than 10% of use; since it did not affect the conclusions of our review, we did not attempt to obtain additional information from clinical experts or payers on this issue.

Price Increase

Over the 12 months (four quarters) for which price changes were assessed, the WAC for pertuzumab increased by approximately 6.08%, while its estimated net price increased by 6.07%. This net price change over the assessed four quarters resulted in an estimated increase in drug spending of $91 million. Estimates of percent change in net price and budget impact due to net price changes in 2022 were provided by the manufacturer.

Review of Clinical Evidence

We reviewed the safety and clinical effectiveness information provided in the FDA label as well as related published literature to assess the baseline evidence on pertuzumab as of January 2021. Following that, we conducted an independent systematic literature review, limited to RCTs, over the 24 months review timeframe (January 2021 – December 2022) (see Appendix Table M1). In addition, we reviewed the RCT and non-RCT information Genentech submitted to us to consider as new clinical information (five references [one conference presentation and four published manuscripts]). However, none of the identified or submitted articles met our criteria of new moderate to high-quality evidence on the benefits and/or harms of pertuzumab (Appendix Table H1). Of the five references submitted by the manufacturer, one article was excluded because it did not meet our UPI review criteria (see Table 3.9). Of the remaining 4 articles, two were considered low quality, and two were considered previously known information about pertuzumab's efficacy (see Table 3.10). As an example, we highlighted one submitted article (Lin et al. 2021) that we classified as low-quality evidence.[22]

Table 3.9. Studies Not Meeting UPI Review Criteria

Reason	Number of References
Study population outside approved label indication	1

For simplicity, we provide a single reason for exclusion of each study, although there may be multiple reasons why a study was excluded.

Table 3.10. Studies Not Meeting Criteria for New Moderate to High-Quality Evidence

Reasons	Number of References
Low-quality evidence	2
Previously known information about pertuzumab related to efficacy	2

Study Not Meeting Criteria for New Moderate- to High-Quality Evidence

The PATRICIA study was a Phase II, open-label, single-arm trial that evaluated the central nervous system (CNS) efficacy of pertuzumab plus high-dose trastuzumab in 39 patients with HER2-positive metastatic breast cancer with brain metastases that had progressed despite prior radiotherapy. [22] Patients received pertuzumab plus high-dose trastuzumab until CNS or systemic disease progression, toxicity, or study withdrawal. Brain responses were assessed by magnetic resonance imaging at weeks 6, 12, 20, and 28 and every 12 weeks. The median (range) treatment duration was 4.5 (0.3-37.3) months. By clinical cutoff, 95% of patients had discontinued treatment, mostly due to CNS progression. Treatment with pertuzumab plus high-dose trastuzumab resulted in 11% of patients achieving the primary endpoint of objective response rate, defined as the proportion of patients with confirmed complete or partial response per Response Assessment in Neuro-Oncology Brain Metastases criteria. No new safety signals were observed.

Reason for Not Meeting Criteria for New Moderate- to High-Quality Evidence:

There are prior assumptions that antibody treatments are unable to penetrate the CNS. The PATRICIA trial presented data showing that pertuzumab plus high-dose trastuzumab may have benefits in patients with CNS metastasis. However, PATRICIA was a small, single-arm trial that provided only low-quality evidence on the CNS benefit of pertuzumab plus high-dose trastuzumab. Furthermore, the PATRICIA trial provides no evidence that adding pertuzumab to high-dose trastuzumab provides additional benefits versus high-dose trastuzumab alone. Under the UPI Protocol, we do not assess the magnitude of benefit in the absence of moderate or high-quality evidence.

Conclusion

After careful review of the evidence, we conclude that pertuzumab (Perjeta®) had a price increase *unsupported* by new clinical evidence.

3.9 Adcetris® (Brentuximab Vedotin, Seagen)

Introduction

Adcetris® (brentuximab vedotin, Seagen) is a CD30-directed monoclonal antibody drug conjugate that is FDA approved in combination with other agents for several indications, including previously untreated Stage III/IV classical Hodgkin lymphoma (cHL), cHL at high risk of relapse or progression as post-autologous hematopoietic stem cell transplantation, systemic anaplastic large cell lymphoma, and primary cutaneous anaplastic large cell lymphoma, all in adult patients.[23] Based on previous information provided by the manufacturer, these approved adult indications all account for greater than 10% of brentuximab vedotin's use.

In November 2022, Adcetris® gained its first pediatric approval for previously untreated high-risk cHL in combination with doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide in patients 2 years and older. The manufacturer did not provide input on the utilization of this new indication. However, per clinical input, this new pediatric indication represents less than 10% of brentuximab vedotin's use.

Price Increase

Over the 12 months (four quarters) for which price changes were assessed, the WAC for brentuximab vedotin increased by approximately 8.69%, while its estimated net price increased by 8.92%. This net price change over the assessed four quarters resulted in an estimated increase in drug spending of $63 million. All pricing information was obtained from SSR Health, LLC.

Review of Clinical Evidence

We reviewed the safety and clinical effectiveness information provided in the FDA label as well as related published literature to assess the baseline evidence on brentuximab vedotin as of January 2021. Following that, we conducted an independent systematic literature review, limited to RCTs, over the 24 months review timeframe (January 2021 – December 2022)(see Appendix Table M1). Our literature search identified 11 articles, none of which met our inclusion criteria of new and potentially moderate- to high-quality evidence on the benefits and/or harms of brentuximab vedotin. Seagen did not submit any additional references to be considered for our review.

Conclusion

After careful review of the evidence, we conclude that brentuximab vedotin (Adcetris®) had a price increase *unsupported* by new clinical evidence.

3.10 Entresto® (Sacubitril/Valsartan, Novartis)

Introduction

Entresto® (sacubitril/valsartan, Novartis) is a twice-daily, single-tablet regimen that combines sacubitril (a neprilysin inhibitor) and valsartan (an angiotensin II receptor blocker).[24] It was approved by the FDA in 2015 and is indicated for reducing the risk of cardiovascular death and hospitalization in patients with chronic heart failure. The label notes that "benefits of sacubitril/valsartan *are most clearly evident in chronic heart failure patients with left ventricular ejection fraction below normal*." Sacubitril/valsartan is also approved for the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients (ages one year and older). Based on the information provided by the manufacturer, only the first indication accounts for greater than 10% of use.

Price Increase

Over the 12 months (four quarters) for which price changes were assessed, the WAC for sacubitril/valsartan increased by approximately 7.96%, while its estimated net price increased by 2.56%. This net price change over the assessed four quarters resulted in an estimated increase in drug spending of $57 million. All pricing information was obtained from SSR Health, LLC.

Review of Clinical Evidence

We reviewed the safety and clinical effectiveness information provided in the FDA label as well as related published literature to assess the baseline evidence on sacubitril/valsartan as of January 2021. Following that, we conducted an independent systematic literature review, limited to RCTs, over the 24 months review timeframe (January 2021 – December 2022) (see Appendix Table M1). In addition, we reviewed the RCT and non-RCT information that Novartis submitted to us to consider as new clinical information (15 references [six conference presentations and nine published manuscripts]).

Of the 15 references submitted by the manufacturer, seven articles were excluded because they did not meet our UPI review criteria. The primary reasons for excluding these studies are provided in Table 3.11 (Appendix table J1 provides additional information on each study). Following our systematic literature review (see Appendix Table M1) and the review of the remaining eight articles submitted by the manufacturer, we identified one reference related to one RCT (PERSPECTIVE) that met our criteria of new and potentially moderate to high-quality evidence on the benefits and/or harms of sacubitril/valsartan (Table 3.13). Additional details on this trial are provided below. The remaining seven references submitted by the manufacturer presented previously known information about sacubitril/valsartan (Table 3.12).

Table 3.11. Studies Not Meeting UPI Review Criteria

Reason	Number of References
Study published outside timeframe of review	4
Indication accounts for less than 10% of use	1
Outcomes not relevant to scope	2

For simplicity, we provide a single reason for exclusion of each study, although there may be multiple reasons why a study was excluded.

Table 3.12. Studies Not Meeting Criteria for New Moderate to High-Quality Evidence

Reasons	Number of References
Previously known information about sacubitril/valsartan related to efficacy	7

Table 3.13. Summary of New Evidence

Baseline Evidence (Before January 2021)	New Evidence
Due to its mechanism of action, the long-term use of sacubitril a neprilysin inhibitor, which is used in combination with valsartan, is hypothesized to increase beta-amyloid plaque deposition in the brain and potentially increase the risk of Alzheimer's disease.[25,26] Upon sacubitril/valsartan's initial approval in 2015, the FDA required Novartis to conduct a postmarketing clinical trial to clarify the long-term neurocognitive safety of neprilysin inhibition by sacubitril.	Results from the 3-year PERSPECTIVE RCT found no evidence of increased risk of cognitive impairment in patients with heart failure on sacubitril/valsartan.[27]

FDA: Food and Drug Administration, RCT: randomized controlled trial

New Evidence

PERSPECTIVE was a non-inferiority RCT that assessed the effect of long-term treatment with sacubitril/valsartan, compared with valsartan only, on cognitive function in patients with heart failure and mildly reduced and preserved ejection fraction (HFmrEF and HFpEF).[27] Patients were treated with either sacubitril/valsartan (n=295) or valsartan (n=297) and were assessed over 3 years on the primary outcome of cognitive function (CogState global cognition composite score [GCCS]) and secondary outcome of beta-amyloid deposition in the brain (assessed using positron emission tomography amyloid [PET] imaging). At 3 years, the least-squares mean change in GCCS from baseline for sacubitril/valsartan was non-inferior to valsartan alone (Cohen's d effect size -0.0277 (95% CI -0.1101 to 0.0778); non-inferiority margin: -0.3). The change from baseline to three years in beta-amyloid accumulation in the brain was less in the sacubitril/valsartan group compared to the valsartan group (-0.0292 (95% CI -0.0593 to 0.0010); P=0.058), although the difference was not statistically significant.

Rating of New Evidence (Quality and Magnitude)

Due to the hypothesized concern that sacubitril/valsartan might be associated with the increased risk of Alzheimer's disease, the FDA required Novartis to conduct a postmarketing clinical trial to evaluate the long-term neurocognitive safety of sacubitril/valsartan. The PERSPECTIVE trial found no evidence of increased risk of beta-amyloid accumulation or cognitive impairment in patients on sacubitril/valsartan. However, the quality of the trial is lowered by susceptibility to bias from high loss to follow-up (28% of participants) and the fact that the findings were only presented at a conference (European Society of Cardiology Congress 2022) and have not yet undergone peer review publication. As such, the PERSPECTIVE trial provides moderate-quality evidence that addresses the concern raised by the FDA.

Conclusion

After careful review of the evidence, we conclude that sacubitril/valsartan (Entresto®) had a price increase *with* new clinical evidence.

4. Medicare Part B

4.1 Darzalex® (Daratumumab, Janssen)

Introduction

Darzalex® (daratumumab, Janssen) is an anti-CD38 monoclonal antibody that first received FDA approval in 2015.[9] It is indicated for the treatment of adult patients with multiple myeloma as both a monotherapy and in combination with other agents. In August of 2020, daratumumab received approval in combination with carfilzomib and dexamethasone in patients with relapsed or refractory multiple myeloma who have received one to three prior lines of therapy.[28]

Price Increase

Over the 12 months (four quarters) for which price changes were assessed, the change in spending per unit of daratumumab increased by approximately 3.67 %. The change in unit price over the assessed four quarters resulted in estimated additional drug spending by Medicare payers and patients of $19.4 million. Assuming up to 20% coinsurance, on average the change in unit price alone would result in up to $481 per year in additional payments by the patient. All pricing information was obtained from the Medicare Part B US government data source.

Review of Clinical Evidence

We reviewed the safety and clinical effectiveness information provided in the FDA label as well as related published literature to assess the baseline evidence on daratumumab as of January 2020. Following that, we conducted an independent systematic literature review, limited to RCTs, over the 24 months review timeframe (January 2020 – December 2021) (see Appendix Table M1). Our literature search identified 34 articles, one of which met our inclusion of new and potentially moderate-to high quality evidence on the benefits and/or harms of daratumumab. Additional details on this trial are provided below (Table 4.1). Janssen did not submit any additional references to be considered for our review.

Table 4.1. Summary of New Evidence

Baseline Evidence (Before January 2020)	New Evidence
Prior to August 2020, daratumumab was not indicated as a triple combination therapy with carfilzomib and dexamethasone for individuals with relapsed or refractory multiple myeloma.	Based on the evidence from the CANDOR RCT, the FDA granted approval for daratumumab in combination with carfilzomib and dexamethasone for the treatment of relapsed or refractory multiple myeloma in adult patients.[29]

FDA: Food and Drug Administration, RCT: randomized controlled trial

New Evidence

CANDOR was a randomized Phase III open-label study that enrolled adult patients with relapsed or refractory multiple myeloma who have received one to three prior lines of therapy.[29,30] In the trial, patients were randomized 2:1 to receive carfilzomib, dexamethasone, and daratumumab (KdD) or carfilzomib and dexamethasone (Kd). The primary efficacy endpoint was progression-free survival (PFS). The trial reported 140 (44.9%) PFS events in the KdD arm compared to 85 (55.2%) PFS events in the Kd arm after a median follow-up of about 27 months.[30] The primary endpoint of PFS was met with a median follow-up of 28.6 months in the KdD arm versus 15.2 months for the Kd arm (hazard ratio: 0.59 [95% CI: 0.45-0.78]). Similarly, the other outcomes, including overall response (75.5% vs. 35.2%, p<0.001) and minimum residual disease-negative rate at 12 months (49.5% vs. 23.1%, p<0.001), favored the KdD group. At the time of data cutoff, median overall survival had not been reached in either group. The rate of treatment discontinuation due to adverse events was similar between the KdD (22%) and Kd groups (25%).

Rating of New Evidence (Quality and Magnitude)

Based on evidence from CANDOR study, the FDA approved daratumumab to be used in combination with carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma who have received one to three prior lines of therapy. The trial was open label and evaluated a surrogate outcome (progression free survival), providing moderate-quality evidence of a substantial benefit for the patient important outcome of survival in patients with relapsed or refractory multiple myeloma who have received one to three prior lines of therapy.

Conclusion

After careful review of the evidence, we conclude that daratumumab (Darzalex®) had a price increase *with* new clinical evidence. The time period of the evidence review for the Medicare Part B assessment (2020-2021) is different from the time period for the commercial assessment (2021-2022) in Section 3.

4.2 Tyvaso® (Treprostinil, United Therapeutics)

Introduction

Tyvaso® (treprostinil, United Therapeutics) is an inhaled prostacyclin mimetic approved by the FDA in 2009.[31] It is indicated for the treatment of adult patients with pulmonary arterial hypertension and the treatment of adult patients with pulmonary hypertension associated with interstitial lung disease (ILD). Based on the information provided by the manufacturer, both indications account for greater than 10% of treprostinil's use.

Price Increase

Over the 12 months (four quarters) for which price changes were assessed, the change in spending per unit of treprostinil increased by approximately 7.38%. The change in unit price over the assessed four quarters resulted in estimated additional drug spending by Medicare payers and patients of $18.2 million. Assuming up to 20% coinsurance, on average the change in unit price alone would result in up to $2,120 per year in additional payments by the patient. All pricing information was obtained from the Medicare Part B US government data source.

Review of Clinical Evidence

We reviewed the safety and clinical effectiveness information provided in the FDA label as well as related published literature to assess the baseline evidence on treprostinil as of January 2020. Following that, we conducted an independent systematic literature review, limited to RCTs, over the 24 months review timeframe (January 2020 – December 2021) (see Appendix Table M1).

In addition, we reviewed the RCT and non-RCT information United Therapeutics submitted to us to consider as new clinical information (seven references [two conference presentations and five published manuscripts]). Of the seven references submitted by the manufacturer, two articles were excluded because they were considered previously known information about treprostinil related to efficacy (see Table 4.2 and Appendix Table K1). The remaining five references, related to one RCT, met our criteria of new and potentially moderate-to-high quality evidence on the benefits and/or harms of treprostinil (Table 4.3).

Table 4.2. Studies Not Meeting Criteria for New Moderate to High-Quality Evidence

Reasons	Number of References
Previously known information about treprostinil related to efficacy	2

Table 4.3. Summary of New Evidence

Baseline Evidence (Before January 2020)	New Evidence
Prior to April 2021, inhaled treprostinil was not indicated for pulmonary hypertension associated with interstitial lung disease.	INCREASE was a pivotal phase II/III RCT that evaluated the efficacy and safety of inhaled treprostinil in adult patients with pulmonary hypertension due to interstitial lung disease.[32-36] Based on the evidence from the INCREASE trial demonstrating clinical benefit in this population, in April 2021, the FDA approved treprostinil as the first therapy to treat patients with pulmonary hypertension associated with interstitial lung disease.[31]

FDA: Food and Drug Administration, RCT: randomized controlled trial

New Evidence

INCREASE was a pivotal, Phase II/III RCT that evaluated inhaled treprostinil in 326 adult patients with pulmonary hypertension due to interstitial lung disease.[32] Patients were randomized to receive either placebo (n=163) or treprostinil (n=163). The primary endpoint was the change in 6-minute walk distance (6-MWD) from the baseline to 16 weeks. Treatment with inhaled treprostinil resulted in improvements from baseline in 6-MWD, with patients in the treprostinil arm achieving a 21.1 meter increase while the placebo arm decreased by 10 meters (P<0.001). Improvements from treprostinil were also observed in NT-proBNP levels, a diagnostic measure for heart failure, and clinical worsening incidence (P<0.001 and P=0.04, respectively). These treatment effects were consistent across subgroups related to disease etiology and severity, baseline hemodynamics, and dose group. The safety profile of treprostinil reflected that of previous studies, and the frequency of adverse events (91-93%) and serious adverse events (23-26%) were similar between both groups. The most frequently reported adverse events included cough, headache, and dyspnea, most of which were mild-to-moderate in severity. Additionally, fewer patients receiving treprostinil compared to placebo experienced negative effects on lung function.

Rating of New Evidence (Quality and Magnitude)

Based on evidence from INCREASE, the FDA expanded the indication of inhaled treprostinil for pulmonary hypertension associated with interstitial lung disease to improve exercise ability. The trial was only 16 weeks, and 21% of patients discontinued treatment prematurely, thus providing moderate-quality evidence on the benefit of treprostinil. We believe the rating of the magnitude of the observed benefit for patients in the INCREASE trial is a close call between “small” and “substantial” because the improvement in the 6-MWD (31.1 m) is close to what experts believe is the minimum clinically important difference (approximately 30 m). The clinical expert we consulted with considered the magnitude of the benefit to be substantial, given the limited treatment options. Therefore, given the FDA approval and the opinions of clinical experts, in the context of the

UPI report, we judge the INCREASE trial as providing moderate-quality evidence of a substantial benefit for treprostinil to improve exercise ability in patients with pulmonary hypertension associated with interstitial lung disease.

Conclusion

After careful review of the evidence, we conclude that treprostinil (Tyvaso®) had a price increase *with* new clinical evidence.

4.3 Nplate® (Romiplostim, Amgen)

Introduction

Nplate® (Romiplostim, Amgen) is a thrombopoietin receptor agonist that is indicated for the treatment of pediatric and adult patients with immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.[37] In January 2021, Nplate® was also approved for the treatment of pediatric and adult patients with hematopoietic subsyndrome of acute radiation syndrome (H-ARS). Based on clinical input, only the ITP indication accounts for greater than 10% of romiplostim's use.

Price Increase

Over the 12 months (four quarters) for which price changes were assessed, the change in spending per unit of romiplostim increased by approximately 6.81%. The change in unit price over the assessed four quarters resulted in estimated additional drug spending by Medicare payers and patients of $17 million. Assuming up to 20% coinsurance, on average the change in unit price alone would result in up to $684 per year in additional payments by the patient. All pricing information was obtained from the Medicare Part B US government data source.

Review of Clinical Evidence

We reviewed the safety and clinical effectiveness information provided in the FDA label as well as related published literature to assess the baseline evidence on romiplostim as of January 2020. Following that, we conducted an independent systematic literature review, limited to RCTs, over the 24 months review timeframe (January 2020 – December 2021) (see Appendix Table M1).

In addition, we reviewed the RCT and non-RCT information Amgen submitted to us to consider as new clinical information (20 references [five conference presentations, one FDA label, and 14 published manuscripts]). However, none of the identified or submitted articles met our criteria of new moderate to high-quality evidence on the benefits and/or harms of romiplostim (Appendix Table L1). Of the 20 references submitted by the manufacturer, 15 articles were excluded because they did not meet our UPI review criteria, while the remaining five articles presented previously known information about romiplostim (see Tables 4.4 and 4.5). As an example, we highlighted an efficacy study conducted in animals that did not meet the UPI criteria.

Table 4.4. Studies Not Meeting UPI Review Criteria

Reason	Number of References
Indication accounts for less than 10% of use	10
Study population outside approved label indication	2
Outcomes not relevant to scope	1
Intervention/comparison not relevant to scope	1
Study Protocol / Editorial / Conference Citation with no Abstract	1

For simplicity, we provide a single reason for exclusion of each study, although there may be multiple reasons why a study was excluded.

Table 4.5. Studies Not Meeting Criteria for New Moderate to High-Quality Evidence

Reasons	Number of References
Previously known information about Nplate® related to efficacy	5

Study Not Meeting UPI Review Criteria

Romiplostim could not be tested for efficacy in patients with H-ARS due to ethical concerns and feasibility issues. As such, the efficacy of Nplate was evaluated in a randomized, blinded, placebo-controlled trial of rhesus monkeys exposed to total body irradiation at a dose that would be lethal in 70% of animals by 60 days of follow-up.[37] These animals were randomized to 24-hour post-irradiation treatment of either a sterile saline (n = 40) or romiplostim (n = 40). The primary efficacy endpoint was survival; monkeys in the romiplostim treatment group had a significantly greater 60-day survival than those in the control group (72.5% versus 32.5%, one-sided p = 0.0002). Nplate was approved under the FDA's Animal Rule, which allows approval based on animal efficacy studies and human safety studies.[38]

Reason(s) for Not Meeting UPI Review Criteria:

We do not believe that the indication of H-ARS accounts for at least 10% of the overall utilization of romiplostim.

Conclusion

After careful review of the evidence, we conclude that romiplostim (Nplate®) had a price increase *unsupported* by new clinical evidence.

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49. Phillippo D, Ades T, Dias S, Palmer S, Abrams KR, Welton NJ. *NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE.* Vol 18: NICE Decision Support Unit, ScHARR, University of Sheffield; 2016.

APPENDIX

Appendix A. Humira®

Appendix Table A1. References Submitted by AbbVie

Citation	Decision
Fendrick, A.M., Mease, P., Davis, M. et al. Continuity of Care Within a Single Patient Support Program for Patients with Rheumatoid Arthritis Prescribed Second or Later Line Advanced Therapy. Adv Ther 40, 990–1004 (2023). https://doi.org/10.1007/s12325-022-02413-w	Study published outside of the timeframe of our review
Bergman, M., Patel, P., Chen, N. et al. Evaluation of Adherence and Persistence Differences Between Adalimumab Citrate-Free and Citrate Formulations for Patients with Immune-Mediated Diseases in the United States. Rheumatol Ther 8, 109–118 (2021). https://doi.org/10.1007/s40744-020-00256-x	Intervention/comparison not relevant to scope
Fendrick, A.M., Macaulay, D., Goldschmidt, D. et al. Higher Medication Adherence and Lower Opioid Use Among Individuals with Autoimmune Disease Enrolled in an Adalimumab Patient Support Program in the United States. Rheumatol Ther 8, 889–901 (2021). https://doi.org/10.1007/s40744-021-00309-9	Intervention/comparison not relevant to scope
Fendrick AM, Brixner D, Rubin DT, et al. Sustained long-term benefits of patient support program participation in immune-mediated diseases: improved medication-taking behavior and lower risk of a hospital visit. Journal of Managed Care & Specialty Pharmacy. 2021;27(8):1086-1095.	Intervention/comparison not relevant to scope
Lauren AV Orenstein, Rahawi K, Danavar A, Lane M, Chovatiya R, Lev-Tov H, Paek SY, Van der Zee HH, Sayed CJ. Presented at Symposium on Hidradenitis Suppurativa (SHSA) congress, Oct 7-9, 2022; Miami, FL, USA. Burden of pain and use of pain medications in patients with Hidradenitis Suppurativa: Real-World data from UNITE	Intervention/comparison not relevant to scope
Mittal, M., Yang, M., Shah, M., Gao, W., Carley, C., & Sherman, B. W. (2021). Impact of Medication Adherence on Healthcare Resource Utilization, Work Loss, and Associated Costs in a Privately Insured Employed Population Treated With Adalimumab in the United States. Journal of occupational and environmental medicine, 63(10), e724–e731. https://doi.org/10.1097/JOM.0000000000002354	Intervention/comparison not relevant to scope

Appendix B. Darzalex®

Appendix Table B1. References Submitted by Janssen

Citation	Decision
N/A	N/A

Appendix C. Ibrance®

Appendix Table C1. References Submitted by Pfizer

Citation	Decision
Goyal RK, Chen H, Abughosh SM, Holmes HM, Candrilli SD, Johnson ML. Overall survival associated with CDK4/6 inhibitors in patients with HR+/HER2– metastatic breast cancer in the United States: A SEER-Medicare population-based study. Cancer 2023;n/a(n/a) doi: https://doi.org/10.1002/cncr.34675.	Study published outside of the timeframe of our review
Park YH, Kim T-Y, Kim GM, et al. Palbociclib plus exemestane with gonadotropin-releasing hormone agonist versus capecitabine in premenopausal women with hormone receptor-positive, HER2-negative metastatic breast cancer (KCSG-BR15-10): a multicentre, open-label, randomised, phase 2 trial. The Lancet Oncology 2019;20(12):1750-59 doi: https://doi.org/10.1016/S1470-2045(19)30565-0.	Study published outside of the timeframe of our review
Rugo H, Liu X, Li B, et al. Abstract P3-01-15: Real-world effectiveness of palbociclib plus aromatase inhibitors (AI) in African American (AA) patients with metastatic breast cancer (MBC). Cancer Research 2023;83(5_Supplement):P3-01-15-P3-01-15 doi: 10.1158/1538-7445.SABCS22-P3-01-15.	Study published outside of the timeframe of our review
Brain E, Pulido M, Paillaud E, et al. Feasibility of palbociclib in women aged 70 and older with resistant and/or pretreated advanced breast cancer in the PALOMAGE study. Cancer Research 2022;82(4 SUPPL) doi: 10.1158/1538-7445.SABCS21-P1-18-04.	Study population outside approved label indication
DeMichele A, Cristofanilli M, Brufsky A, et al. Comparative effectiveness of first-line palbociclib plus letrozole versus letrozole alone for HR+/HER2-metastatic breast cancer in US real-world clinical practice. Breast Cancer Res 2021;23(1):37 doi: 10.1186/s13058-021-01409-8.	Low-quality evidence
Law E, Gavanji R, Walsh S, Haltner A, McTavish R, Cameron C. Palbociclib versus abemaciclib in HR+/HER2- advanced breast cancer: an indirect comparison of patient-reported end points. Journal of Comparative Effectiveness Research 2021;11(2):109-20 doi: 10.2217/cer-2021-0221.	Low-quality evidence
Rugo HS, Liu X, Li B, McRoy L, Layman R, Brufsky A. 236P Real-world comparative effectiveness of palbociclib plus letrozole vs letrozole in older patients with metastatic breast cancer. Annals of Oncology 2021;32:S462 doi: 10.1016/j.annonc.2021.08.519.	Low-quality evidence
Brufsky A, Liu X, Li B, McRoy L, Layman RM. Real-world effectiveness of palbociclib plus letrozole vs letrozole alone for metastatic breast cancer with lung or liver metastases: Flatiron Database analysis. Front Oncol 2022;12:865292 doi: 10.3389/fonc.2022.865292.	Previously known information about palbociclib related to efficacy
Cristofanilli M, Rugo HS, Im SA, et al. Overall survival with palbociclib and fulvestrant in women with HR+/HER2- ABC: updated exploratory analyses of PALOMA-3, a double-blind, phase III randomized study. Clin Cancer Res 2022;28(16):3433-42 doi: 10.1158/1078-0432.Ccr-22-0305.	Previously known information about palbociclib related to efficacy
Finn RS, Rugo HS, Diéras V, et al. Overall survival (OS) with first-line palbociclib plus letrozole (PAL+LET) versus placebo plus letrozole (PBO+LET) in women with estrogen receptor–positive/human epidermal growth factor receptor 2–negative advanced breast cancer (ER+/HER2− ABC): analyses from PALOMA-2. American Society of Clinical Oncology (ASCO). Chicago, IL, 2022.	Previously known information about palbociclib related to efficacy

Citation	Decision
Gao JJ, Cheng J, Prowell TM, et al. Overall survival in patients with hormone receptor-positive, HER2-negative, advanced or metastatic breast cancer treated with a cyclin-dependent kinase 4/6 inhibitor plus fulvestrant: a US Food and Drug Administration pooled analysis. The Lancet Oncology 2021;22(11):1573-81 doi: https://doi.org/10.1016/S1470-2045(21)00472-1.	Previously known information about palbociclib related to efficacy
Ha MJ, Singareeka Raghavendra A, Kettner NM, et al. Palbociclib plus endocrine therapy significantly enhances overall survival of HR+/HER2- metastatic breast cancer patients compared to endocrine therapy alone in the second-line setting: A large institutional study. Int J Cancer 2022;150(12):2025-37 doi: 10.1002/ijc.33959.	Previously known information about palbociclib related to efficacy
Hu X, Broughton E, Li W, et al. Patient-reported quality of life in patients with hormone receptor–positive/human epidermal growth factor receptor 2–negative advanced breast cancer treated with palbociclib plus letrozole: results From PALOMA-4 [poster]. European Society for Medical oncology (ESMO) Congress. Virtual, 2022.	Previously known information about palbociclib related to efficacy
Rocque G, Blum JL, Ji Y, et al. 266P Real-world quality of life (QoL) in patients with HR+/HER2-advanced breast cancer (ABC) treated with palbociclib: Final clinical outcome assessment (COA) analysis from POLARIS. Annals of Oncology 2022;33:S659 doi: https://doi.org/10.1016/j.annonc.2022.07.305.	Previously known information about palbociclib related to efficacy
Rugo HS, Brufsky A, Liu X, et al. Real-world study of overall survival with palbociclib plus aromatase inhibitor in HR+/HER2- metastatic breast cancer. NPJ Breast Cancer 2022;8(1):114 doi: 10.1038/s41523-022-00479-x.	Previously known information about palbociclib related to efficacy
Finn RS, Rugo HS, Gelmon KA, et al. Long-Term Pooled Safety Analysis of Palbociclib in Combination with Endocrine Therapy for Hormone Receptor-Positive/Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Updated Analysis with up to 5 Years of Follow-Up. Oncologist 2021;26(5):e749-e55 doi: 10.1002/onco.13684.	Previously known information about palbociclib related to safety

Appendix D. Prolia®

Appendix Table D1. References Submitted by Amgen

Citation	Decision
Curtis JR, Arora T, Liu Y, Lin TC, Spangler L, Brunetti VC (2023). Comparative Effectiveness of Denosumab versus Alendronate among Postmenopausal Women with Osteoporosis in the U.S. Medicare Program [Abstract]. World Congress on Osteoperosis, Osteoarthritis and Musculoskeletal Diseases (2023).	Study published outside of the timeframe of our review
Hans, D., McDermott, M., Huang, S. et al. Long-term effect of denosumab on bone microarchitecture as assessed by tissue thickness–adjusted trabecular bone score in postmenopausal women with osteoporosis: results from FREEDOM and its open-label extension. Osteoporos Int 34, 1075–1084 (2023). https://doi.org/10.1007/s00198-023-06708-8	Study published outside of the timeframe of our review
Li, N., Cornelissen, D., Silverman, S. et al. An Updated Systematic Review of Cost-Effectiveness Analyses of Drugs for Osteoporosis. PharmacoEconomics 39, 181–209 (2021). https://doi.org/10.1007/s40273-020-00965-9. [Epub available 2020]	Study published outside of the timeframe of our review
Johnson, B., Lai, E.CC., Ou, Ht. et al. Real-world cost-effectiveness of denosumab for the treatment of postmenopausal osteoporosis in Taiwan. Arch Osteoporos 16, 155 (2021). https://doi.org/10.1007/s11657-021-01020-6	Intervention/comparison not relevant to scope
Kim M, McGrath L, Pritchard D, Samai P, Lin J, Stad R, Spangler L, McDermott M, Bradbury B, Brookhart M. Comparative Effectiveness of Osteoporosis (OP) Therapies Among a Population of Postmenopausal (PM) Women in the United States (U.S.) [abstract]. Arthritis Rheumatol. 2022; 74 (suppl 9). https://acrabstracts.org/abstract/comparative-effectiveness-of-osteoporosis-op-therapies-among-a-population-of-postmenopausal-pm-women-in-the-united-states-u-s/.	Low-quality evidence
Singer, A., Liu, J., Yan, H. et al. Treatment patterns and long-term persistence with osteoporosis therapies in women with Medicare fee-for-service (FFS) coverage. Osteoporos Int 32, 2473–2484 (2021). https://doi.org/10.1007/s00198-021-05951-1	Low-quality evidence
Choo, Y.W., Mohd Tahir, N.A., Mohamed Said, M.S. et al. Cost-effectiveness of Denosumab for the Treatment of Postmenopausal Osteoporosis in Malaysia. Osteoporos Int 33, 1909–1923 (2022). https://doi.org/10.1007/s00198-022-06444-5	Previously known information about denosumab related to efficacy
Kang J-Y, Choi L, Johnson B, Yang H. Cost-Effectiveness of Denosumab for the Treatment of Postmenopausal Osteoporosis in South Korea. J Bone Metab. 2022;29(2):83-92.	Previously known information about denosumab related to efficacy
Luo, C., Qin, SX., Wang, QY. et al. Cost-effectiveness analysis of five drugs for treating postmenopausal women in the United States with osteoporosis and a very high fracture risk. J Endocrinol Invest 46, 367–379 (2023). https://doi.org/10.1007/s40618-022-01910-7. [Epub available 2022]	Previously known information about denosumab related to efficacy
Nargesi S, Husseini Barghazan S, Sani'ee N, Rashki Kemmak A. Economic Evaluation of Denosumab for Treatment of Postmenopausal Osteoporosis: A Systematic Review. Iran J Public Health. 2022;51(7):1502-1512.	Previously known information about denosumab related to efficacy
Spangler L, Nielson C, Brookhart M, Hernandez R, Stad R, Lin J. Myocardial Infarction and Stroke Risks Among Patients Who Initiated Treatment with Denosumab or Zoledronic Acid for Osteoporosis [abstract]. Arthritis Rheumatol. 2022; 74 (suppl 9). https://acrabstracts.org/abstract/myocardial-	Previously known information about denosumab related to efficacy

Citation	Decision
infarction-and-stroke-risks-among-patients-who-initiated-treatment-with-denosumab-or-zoledronic-acid-for-osteoporosis/.	
You R, Liu J, Ke L, Wan M, Zhang Y, Yu G and Mori T (2022) Cost-Effectiveness of Sequential Denosumab/Zoledronic Acid Compared With Zoledronic Acid Monotherapy for Postmenopausal Osteoporotic Women in China. Front. Pharmacol. 13:816248. doi: 10.3389/fphar.2022.816248	Previously known information about denosumab related to efficacy
You R, Mori T, Ke L, et al. Which injected antiosteoporotic medication is worth paying for? A cost-effectiveness analysis of teriparatide, zoledronate, ibandronate, and denosumab for postmenopausal osteoporotic women in China. Menopause. 2021;29(2):210-218. Published 2021 Dec 20. doi:10.1097/GME.0000000000001911	Previously known information about denosumab related to efficacy

Appendix E. Jakafi®

Appendix Table E1. References Submitted by Incyte

Citation	Decision
DeFilipp A et al. Prolonged post-transplant ruxolitinib therapy is associated with protection from severe graft versus host disease after allogeneic HCT [poster]. Presented at: Tandem Meetings; April 23- 26, 2022; Salt Lake City, UT.	Study population outside approved label indication
Hobbs G et al. A Phase II Study of Ruxolitinib Pre-, during- and Post-Hematopoietic Celltransplantation for Patients with Primary or Secondary Myelofibrosis. Blood 2021; 138 (Supplement 1): 169. doi: https://doi.org/10.1182/blood-2021-146330	Study population outside approved label indication
Locatelli F et al. Ruxolitinib in Pediatric Patients with Treatment-Naïve or Steroid-Refractory Acute Graft-Versus-Host Disease: Primary Findings from the Phase I/II REACH4 Study. Blood 2022; 140 (Supplement 1): 1376–1378. doi: https://doi.org/10.1182/blood-2022-155708	Study population outside approved label indication
Tasian SK et al. A Phase 2 Study of Ruxolitinib with Chemotherapy in Children with Philadelphia Chromosome-like Acute Lymphoblastic Leukemia (AALL1521/INCB18424-269): Biologic Characteristics and Minimal Residual Disease Response of Patients with Non-CRLF2-Rearranged JAK Pathway Alterations. Blood 2022; 140 (Supplement 1): 6117–6118. doi: https://doi.org/10.1182/blood-2022-164699	Study population outside approved label indication
Verstovsek S, Amoloja T, Scherber RM, Yu J. Real-world patient characteristics and treatment patterns of ruxolitinib among patients with advanced essential thrombocythemia at community clinical practice. Leukemia Research. 2021;110:106711.	Study population outside approved label indication
Gerds AT et al. Real-world healthcare utilization, costs and overall survival among patients with intermediate- to high-risk myelofibrosis in the United States: ruxolitinib exposed vs unexposed [poster]. Presented at: Annual Meeting of the Academy of Managed Care Pharmacy; April 12-16, 2021; Virtual.	Low-quality evidence
Verstovsek S et al. (2022) Changes in the incidence and overall survival of patients with myeloproliferative neoplasms between 2002 and 2016 in the United States, Leukemia & Lymphoma, 63:3, 694-702, DOI: 10.1080/10428194.2021.1992756	Low-quality evidence
Verstovsek S et al. Real-world survival of US patients with intermediate- to high-risk myelofibrosis: impact of ruxolitinib approval. Ann Hematol 101, 131–137 (2022). https://doi.org/10.1007/s00277-021-04682-x	Low-quality evidence

Appendix F. Xifaxan®

Appendix Table F1. References Submitted by Bausch Health

Citation	Decision
N/A	N/A

Appendix G. Xgeva®

Appendix Table G1. References Submitted by Amgen

Citation	Decision
N/A	N/A

Appendix H. Perjeta®

Appendix Table H1. References Submitted by Genentech

Citation	Decision
Yamamoto Y, Iwata H, Taira N, et al. Pertuzumab retreatment for HER2-positive advanced breast cancer: A randomized, open-label phase III study (PRECIOUS). Cancer Sci. 2022;113(9):3169-3179.10.1111/cas.15474	Study population outside approved label indication
Lin NU, Pegram M, Sahebjam S, et al. Pertuzumab Plus High-Dose Trastuzumab in Patients With Progressive Brain Metastases and HER2-Positive Metastatic Breast Cancer: Primary Analysis of a Phase II Study. J Clin Oncol. 2021;39(24):2667-2675.10.1200/JCO.20.02822	Low-quality evidence
Takahashi M, Ohtani S, Nagai SE, et al. The efficacy and safety of pertuzumab plus trastuzumab and docetaxel as a first-line therapy in Japanese patients with inoperable or recurrent HER2- positive breast cancer: the COMACHI study. Breast Cancer Res Treat. 2021;185(1):125- 134.10.1007/s10549-020-05921-x	Low-quality evidence
Loibl S, Jassem J, Sonnenblick A, et al. VP6-2022: Adjuvant pertuzumab and trastuzumab in patients with early HER-2 positive breast cancer in APHINITY: 8.4 years' follow-up. Annals of Oncology. 2022;33(9):986-987.10.1016/j.annonc.2022.06.009	Previously known information about pertuzumab related to efficacy
Swain SM, Macharia H, Cortes J, et al. Event-Free Survival in Patients with Early HER2-Positive Breast Cancer with a Pathological Complete Response after HER2-Targeted Therapy: A Pooled Analysis. Cancers (Basel). 2022;14(20).10.3390/cancers14205051	Previously known information about pertuzumab related to efficacy

Appendix I. Adcetris®

Appendix Table I1. References Submitted by Seagen

Citation	Decision
N/A	N/A

Appendix J. Entresto®

Appendix Table J1. References Submitted by Novartis

Citation	Decision
Haseeb M, Nouman Aslam M, Avanteeka F, et al. (March 20, 2023) Comparison of Efficacy and Safety of Angiotensin Receptor-Neprilysin Inhibitors in Patients With Heart Failure With Reduced Ejection Fraction: A Meta-Analysis. Cureus 15(3): e36392. DOI 10.7759/cureus.36392	Study published outside of the timeframe of our review
Shen X, Schwartz T, Suillvan G, Adelsberg M, Francis M et al. (2023) Sacubitril/Valsartan in Medicare Alternative Payment Models. Am J Accountable Care. 2023;11(1):5-17. https://doi.org/10.37765/ajac.2023.89339	Study published outside of the timeframe of our review
Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. New England Journal of Medicine. 2019;381(17):1609-1620.	Study published outside of the timeframe of our review
Vaduganathan M, Mentz RJ, Claggett BL, Miao ZM, Kulac IJ, Ward JH, Hernandez AF, Morrow DA, Starling RC, Velazquez EJ, Williamson KM. Sacubitril/valsartan in heart failure with mildly reduced or preserved ejection fraction: a pre-specified participant-level pooled analysis of PARAGLIDE-HF and PARAGON-HF. European Heart Journal. 2023 May 21.	Study published outside of the timeframe of our review
PANORAMA-HF trial (Primary results): ARNI in paediatric patients with LV systolic dysfunction. Shaddy, R. et al. Presented at European Society of Cardiology, Barcelona, Spain, August 27, 2022	Indication accounts for less than 10% of use
Shen X, Sullivan G, Adelsberg M, Francis M, Schwartz T et al. (2021) 90-Day Episodic costs fo heart failure with reduced ejection fraction (HFREF) patients receiving sacubitril/valsartan compared to other treatment within the Medicare bundled payment care iniative (BPCI) model 2, 2016-2018. (#1035-05) American Heart Association Atlanta, Georgia May 15, 2021	Outcomes not relevant to scope
Shen X, Sullivan G, Adelsberg M, Francis M, Schwartz T et al. (2021) The association between sacubitril/valsartan utilization and healthcare costs for patients with heart failure with reduced ejection fraction (HFREF) in Medicare shared savings program participants in 2018. (#902-14) American Heart Association Atlanta, Georgia May 16, 2021.	Outcomes not relevant to scope
Basile C, Paolillo S, Gargiulo P, et al. Sacubitril/valsartan reduces cardiac decompensation in heart failure with preserved ejection fraction: a meta-analysis. J Cardiovasc Med (Hagerstown). 2023;24(1):44-51. doi:10.2459/JCM.0000000000001411. [Epub available 2022].	Previously known information about sacubitril/valsartan related to efficacy
Blumer V, Choi S, Greene SJ, et al. Abstract 10738: Comparative Outcomes of Sacubitril/Valsartan Use Among Medicare Beneficiaries NaïVe to Renin-angiotensin System Inhibitors and Hospitalized with Heart Failure. Circulation. 2021;144(Suppl_1):A10738-A10738.	Previously known information about sacubitril/valsartan related to efficacy
Chapman B, Hellkamp AS, Thomas LE, et al. Angiotensin Receptor Neprilysin Inhibition and Associated Outcomes by Race and Ethnicity in Patients With Heart Failure With Reduced Ejection Fraction: Data From CHAMP-HF. Journal of the American Heart Association. 2022;11(12):e022889.	Previously known information about sacubitril/valsartan related to efficacy
Greene SJ, Choi S, Lippmann SJ, et al. Clinical Effectiveness of Sacubitril/Valsartan Among Patients Hospitalized for Heart Failure With Reduced Ejection Fraction. Journal of the American Heart Association. 2021;10(16):e021459.	Previously known information about sacubitril/valsartan related to efficacy

Citation	Decision
Pieske B, Wachter R, Shah SJ, et al. Effect of Sacubitril/Valsartan vs Standard Medical Therapies on Plasma NT-proBNP Concentration and Submaximal Exercise Capacity in Patients With Heart Failure and Preserved Ejection Fraction: The PARALLAX Randomized Clinical Trial. JAMA. 2021;326(19):1919–1929. doi:10.1001/jama.2021.18463	Previously known information about sacubitril/valsartan related to efficacy
Rahhal A, Kasem M, Orabi B, et al. Effectiveness of Sacubitril/Valsartan in Heart Failure with Reduced Ejection Fraction Using Real-World Data: An Updated Systematic Review and Meta-Analysis. Current Problems in Cardiology. 2023;48(1):101412. [Epub available 2022].	Previously known information about sacubitril/valsartan related to efficacy
Thomas, M., Khariton, Y., Fonarow, G. C., Arnold, S. V., Hill, L., Nassif, M. E., Chan, P. S., Butler, J., Thomas, L., DeVore, A. D., Hernandez, A. F., Albert, N. M., Patterson, J. H., Williams, F. B., & Spertus, J. A. (2021). Association between sacubitril/valsartan initiation and real-world health status trajectories over 18 months in heart failure with reduced ejection fraction. ESC heart failure, 8(4), 2670–2678. https://doi.org/10.1002/ehf2.13298	Previously known information about sacubitril/valsartan related to efficacy

Appendix K. Tyvaso®

Appendix Table K1. References Submitted by United Therapeutics

Citation	Decision
Shapiro, S., Mandras, S., Restrepo-Jaramillo, R., Shen, E., Broderick, M., Rao, Y., Lee, D. and Nelsen, A.C. (2021), Survival and drug persistence in patients receiving inhaled treprostinil at doses greater than 54 µg (nine breaths) four times daily. Pulmonary Circulation, 11: 1-7 20458940211052228. https://doi.org/10.1177/20458940211052228	Previously known information about treprostinil related to efficacy
Tonelli, A.R., Sahay, S., Gordon, K.W., Edwards, L.D., Allmon, A.G., Broderick, M. and Nelsen, A.C. (2020), Impact of inhaled treprostinil on risk stratification with noninvasive parameters: a post hoc analysis of the TRIUMPH and BEAT studies. Pulmonary Circulation, 10: 1-10 2045894020977025. https://doi.org/10.1177/2045894020977025	Previously known information about treprostinil related to efficacy

Appendix L. Nplate®

Appendix Table L1. References Submitted by Amgen

Citation	Decision
Bunin D, Bakke J, Green CE, Javitz HS, Fielden M, Chang PY. (2020) Romiplostim (Nplate®) as an effective radiation countermeasure to improve survival and platelet recovery in mice, International Journal of Radiation Biology, 96:1, 145-154, DOI: 10.1080/09553002.2019.1605465	Indication accounts for less than 10% of use
Bunin DI, Javitz HS, Gahagen J, et al. Survival and Hematologic Benefits of Romiplostim After Acute Radiation Exposure Supported FDA Approval Under the Animal Rule. International Journal of Radiation Oncology, Biology, Physics. 2023 May:S0360-3016(23)00449-2. DOI: 10.1016/j.ijrobp.2023.05.008. PMID: 37224926.	Indication accounts for less than 10% of use
Doshi S, Jones Z, Pritchard-Bell A, Park J, Gisleskog PO. Extrapolation and Justification of Nplate Dosing to Improve Overall Survival (OS) in Acute Radiation Syndrome. Blood 2020; 136 (Supplement 1): 15–16. doi: https://doi.org/10.1182/blood-2020-139177	Indication accounts for less than 10% of use
Jones Z, Olsson Gisleskog P, Pritchard-Bell A, Doshi S. A time to event model to predict overall survival in non-human primates with acute radiation syndrome [Abstract]. Presented at: 11th American Conference on Pharmacometrics, 2020	Indication accounts for less than 10% of use
Nishida T, Yamaguchi M, Tatara Y, Kashiwakura I. Proteomic changes by radio-mitigative thrombopoietin receptor agonist romiplostim in the blood of mice exposed to lethal total-body irradiation. Int J Radiat Biol. 2020;96(9):1125-1134. doi:10.1080/09553002.2020.1787546	Indication accounts for less than 10% of use
Pritchard-Bell A, Jones Z, Doshi S. Estimating Impact of Acute Radiation Exposure on PKPD of Romiplostim in Rhesus Monkeys [Abstract]. Presented at: 11th American Conference on Pharmacometrics, 2020	Indication accounts for less than 10% of use
Wong K, Chang PY, Fielden M, et al. Pharmacodynamics of romiplostim alone and in combination with pegfilgrastim on acute radiation-induced thrombocytopenia and neutropenia in non-human primates. Int J Radiat Biol. 2020;96(1):155-166. doi:10.1080/09553002.2019.1625488	Indication accounts for less than 10% of use
Yamaguchi M, Hirouchi T, Yoshioka H, Watanabe J, Kashiwakura I. Diverse functions of the thrombopoietin receptor agonist romiplostim rescue individuals exposed to lethal radiation. Free Radic Biol Med. 2019;136:60-75. doi:10.1016/j.freeradbiomed.2019.03.023	Indication accounts for less than 10% of use
Yamaguchi M, Suzuki M, Funaba M, Chiba A, Kashiwakura I. Mitigative efficacy of the clinical dosage administration of granulocyte colony-stimulating factor and romiplostim in mice with severe acute radiation syndrome. Stem Cell Res Ther. 2020;11(1):339. Published 2020 Aug 3. doi:10.1186/s13287-020-01861-x	Indication accounts for less than 10% of use
Nolla M, Aladjidi N, Leblanc T, Fernandes H, Ducassou S, Fahd M, et al. Thrombopoietin receptor agonists as an emergency treatment for severe newly diagnosed immune thrombocytopenia in children. Blood 2021; 137 (1): 138–141. doi: https://doi.org/10.1182/blood.2020006807	Study population outside approved label indication
Roumier M, Le Burel S, Audia S, Chauchet A, Gousseff M, Hamidou M, et al. (2021), High dose romiplostim as a rescue therapy for adults with severe bleeding and refractory immune thrombocytopenia. Am J Hematol, 96: E43-E46. https://doi.org/10.1002/ajh.26040	Study population outside approved label indication
Cooper N, Hill QA, Grainger J, et al. Tapering and Discontinuation of Thrombopoietin Receptor Agonist Therapy in Patients with Immune	Outcomes not relevant to scope

Citation	Decision
Thrombocytopenia: Results from a Modified Delphi Panel. Acta Haematol. 2021;144(4):418-426. doi:10.1159/000510676	
Hatfield M, Manjelievskaia J, Evans KA, Chan PK, Shah N, Saad H. Treatment patterns and bleeding events among patients with immune thrombocytopenia based on duration of corticosteroid treatment [Abstract]. Blood 2020; 136 (Supplement 1): 40–41. doi: https://doi.org/10.1182/blood-2020-141457	Intervention/comparison not relevant to scope
Chen F, McDonald V, Newland A. (2021): Experts' review: the emerging roles of romiplostim in immune thrombocytopenia (ITP), Expert Opinion on Biological Therapy, DOI: 10.1080/14712598.2021.1960979	Study Protocol / Editorial / Conference Citation with no Abstract
Food and Drug Administration. FDA Prescribing Information for Nplate (2021)	Indication accounts for less than 10% of use
Bowers C, Mytych DT, Lawrence T, et al. Assessment of romiplostim immunogenicity in pediatric patients in clinical trials and in a global postmarketing registry. Blood Adv. 2021;5(23):4969-4979. doi:10.1182/bloodadvances.202100510	Previously known information about romiplostim related to efficacy
Gibiansky E, Serrano Castillo F, Saad H, Fung-Sing Chow V, Doshi S; Assessing Romiplostim Dose and Platelet Response-Guided Titration to Support Use of Romiplostim in ITP Patients Less Than 12 Months from Diagnosis. Blood 2021; 138 (Supplement 1): 4221. doi: https://doi.org/10.1182/blood-2021-153066	Previously known information about romiplostim related to efficacy
Newland A, Viallard JF, López Fernández MF, Eisen M, Saad H, Hippenmeyer J, et al. Romiplostim for the Treatment of Adult Patients with Newly Diagnosed or Persistent Immune Thrombocytopenia: Subgroup Analysis from a Phase 2 Study [Abstract]. Presented at: American Society of Hematology Congress, 2021	Previously known information about romiplostim related to efficacy
Skopec B, Sninska Z, Tzvetkov N, Ivanushkin V, Björklöf K, Hippenmeyer J, et al. (2021) Effectiveness and safety of romiplostim among patients with newly diagnosed, persistent and chronic ITP in routine clinical practice in central and Eastern Europe: an analysis of the PLATON study, Hematology, 26:1, 497-502, DOI:10.1080/16078454.2021.1948209	Previously known information about romiplostim related to efficacy
Snell Taylor, S.J., Nielson, C.M., Breskin, A. et al. Effectiveness and Safety of Romiplostim Among Patients with Newly Diagnosed, Persistent and Chronic Immune Thrombocytopenia in European Clinical Practice. Adv Ther 38, 2673–2688 (2021). https://doi.org/10.1007/s12325-021-01727-5	Previously known information about romiplostim related to efficacy

Appendix M. ICER Systematic Literature Review

Appendix Table M1. ICER Systematic Literature Review Results

Drug	Search Yield	References Screened in Full-Text	New Evidence Identified
Humira®	72	1	0
Darzalex®	42	3	1
Ibrance®	32	0	0
Prolia®	47	0	0
Jakafi®	30	1	1
Xifaxan®	19	0	0
Xgeva®	47	0	0
Perjeta®	37	0	0
Adcetris®	11	1	0
Entresto®	69	0	0
Tyvaso®	12	1	1
Nplate®	2	0	0

Evidence identified for Jakafi® and Tyvaso® overlaps with references submitted by their respective manufacturers.

Appendix Table M2. Sample Search Strategy in Embase

((Prolia OR denosumab) AND (('Randomized controlled trial' OR 'randomized control trial' OR 'controlled clinical trial' OR RCT) NOT ('case report' OR 'human tissue' OR 'practice guideline' OR questionnaire OR chapter OR 'conference review' OR editorial OR letter OR note OR review OR 'short survey' OR animal OR nonhuman OR 'animal experiment')) AND 2021/01/01:2022/12/31[dp])

Appendix N. ICER Responses to Manufacturer Comments

General Evidence Response

General Evidence Response (GER): Many public comments from manufacturers focused on the evaluation and interpretation of evidence within the ICER UPI Report. The following is a combined response to such questions and comments. This should allow all stakeholders to see, in a single place, how ICER is thinking about evidence with regard to the UPI Report. Additionally, to avoid redundancy, we will respond to some individual public comments by referencing one or more of the sections below.

1. New Clinical Evidence
    a. Over a two-year period, there will virtually always be new published information about widely used medications. However, for ICER to consider such information as potentially providing support for a price increase, there must be some question that was evaluated such that there is an answer that could be counted, *a priori*, as **not** supporting a price increase had the results come out differently. For instance, if the HR for survival with a therapy has been shown to be 0.72 with four years of follow-up and at eight years of follow-up the HR is now calculated to be 0.75, there must have been a prior belief about what that HR might have been at eight years for this to be assessed as to whether it supports a price increase. Without that prior belief, we are unable to know whether this is a favorable or unfavorable result for the drug under consideration.
    b. New evidence must provide information different from what was previously believed to support a price increase. In the example above, if it were assumed that the HR for survival would persist over time, and at eight years of follow-up the HR was again 0.75, this would not be considered support. In contrast, had there been serious reasons for concern that the effect of therapy decreased substantially over time, a HR of 0.75 at eight years could provide support.
    c. High-quality evidence about a therapy does not provide high-quality evidence about the background therapy that was used in the clinical trial. For example, a new RCT of a therapy for osteoporosis that included calcium and vitamin D in both the intervention and placebo arms of the trial does not provide new evidence for calcium and vitamin D even if the new therapy is only approved when used with such background treatment.

2. Real-World Evidence (RWE)
    a. ICER applies the same evidentiary standards to RWE that it applies to all other forms of evidence and is happy to consider RWE as part of the UPI Report.
    b. High-quality RWE can be particularly valuable in assessing effectiveness of therapies and issues around adherence.
3. Quality of Observational Evidence
    a. As noted in the UPI Protocol, as part of the UPI Report process, ICER only reviewed observational studies that were submitted by manufacturers.
    b. As noted in the UPI Protocol, ICER is using GRADE to assess quality of evidence. Most high-quality comparative observational studies generate only low-quality evidence using GRADE for the comparison being assessed. That is, the quality of the observational studies is only one factor that goes into assessing the quality of the evidence provided by those studies. Factors that can sometimes increase the quality of evidence from observational studies to "high-quality" include large (or very large) magnitude of effect, dose response, or all plausible residual confounding working opposite to the effect being seen.
4. Modeling and Meta-Analyses
    a. Models and meta-analyses provide ways of interpreting and combining evidence but are not new evidence in and of themselves. Occasionally, models and meta-analyses lead to a new understanding of evidence that is substantially different from what was previously believed. Under these circumstances, models and meta-analyses could contribute as "new evidence" within the UPI Report.
    b. Economic outcomes are explicitly part of the UPI process and can count as new clinical evidence if the results are different from what had been previously believed.
5. Importance of Studies
    a. As discussed in the Introduction, ICER recognizes that studies and trials that confirm prior beliefs, increase quality of evidence, and examine new aspects of a therapy's benefits are vitally important. Nothing in the UPI Report should be taken to suggest that studies that fail to support large price increases of the most expensive drugs used in the US are somehow not worth having been performed. That is not the bar that UPI is using. The UPI Report is assessing the fairness of price increases, not the value of research.
    b. Studies evaluating the benefits of a therapy in a small population are also clearly important. ICER does not believe, however, that demonstrating new benefits in a small population justifies large price increases in the most expensive drugs.

#	Comment	Response/Integration
	AbbVie	
1.	**AbbVie contends that the methodology and purpose of this assessment remains flawed. With intrinsic limitations of evaluating evidence, uncertainty of net price, and incomplete measurements of value, ICER's UPI report could inappropriately impact patient access to medicines and lead to oversimplified pricing policies, and value assessment decisions.** **AbbVie believes that ICER's UPI analysis is subjective. ICER does not set any specific parameters in their methodology for exactly what new clinical evidence would support a price increase of a certain magnitude, nor are there industry standards for doing so. Additionally, we believe ICER utilizes an opaque and inconsistent process to determine whether sufficient clinical evidence exists to support price increases. Given this lack of scientific rigor, we maintain that ICER's findings in the UPI report are merely ICER's opinion and should not be used to determine access to treatment or to inform policy decisions.**	As noted in our protocol, ICER uses GRADE in making judgement about quality of evidence. Judgments about whether benefits are small or substantial are necessarily subjective.
2.	AbbVie believes that the determination of value demands a comprehensive scientific approach encompassing the totality of available clinical, economic, and humanistic evidence. Objective analysis of available randomized studies and real-world evidence is required, including long-term longitudinal studies evaluating economic and humanistic outcomes (i.e., health care resource utilization, work productivity, patient reported outcomes and patient preference). In contrast, value assessments, such as those put forth by ICER, utilize an incomplete approach to evidence and opinion-based assessments, and as a direct result, provide an incomplete answer to whether a given treatment offers value.1 As one example of how ICER does not perform full value assessments for the therapies selected for evaluation within its UPI report, ICER excludes indications that represent less than 10% of a product's utilization. In doing so, ICER is potentially minimizing the impact of a product on rare conditions with small populations where therapeutic options are often limited such as hidradenitis suppurativa (known as "HS"), a rare orphan disease for which HUMIRA is indicated to treat.	It is important to note that the ICER UPI report is not a value assessment report. It is also not intended to determine whether a price increase for a drug is fully justified by new clinical evidence or meets an ICER health-benefit price benchmark. Instead, the analyses focused on whether substantial new evidence existed that could justify a price increase. By identifying whether there is, or is not, new evidence of improved safety or effectiveness for drugs with substantial price increases, we hope to take an important first step in providing the public and policymakers with information they can use to advance the public debate on drug price increases. Please also see GER 5b
3.	Revealingly, ICER itself admits that its approach is limited and not comprehensive, via a disclosure written within its UPI Protocol: *"…ICER does not currently have the capacity to perform full economic analyses on the large number of therapies that will be subject to analysis as part of this report process, nor would the time needed to develop full ICER reports (at least eight months) provide information in a useful timeframe for the public and policymakers."2* In their Report on US Value	ICER's UPI report is not a value assessment report, therefore, the cited comments are not relevant to its purpose. As described in the report, we look to see whether there is new evidence that may justify a price increase, not whether the degree of the price increase itself is reasonable given new evidence. As such, the existence, or lack thereof, of a standard to determine whether the amount of a price increase is reasonable

#	Comment	Response/Integration
	Assessment Framework, the ISPOR Special Task Force warns of this risk, *"…attempting to simplify the problem of value assessment, [value] frameworks could end up making ad hoc assumptions and simplifications not supported by theory or evidence, and thus may not deliver promised value."3* Despite ICER's own recognition that it lacks the capacity to perform the full economic analyses that would be necessary to arrive at the conclusions in this report and the feedback from multiple stakeholders over the last several years regarding the flawed methodology, the UPI report is published every year without addressing these limitations. Further, ICER disregards the fact that there are no recognized scientific or even ICER-defined standards to determine how much of a price increase is supported based on new clinical evidence. The result of this opaque process is an UPI report that seems to be based on the judgement of ICER reviewers determining whether they feel a price increase is supported based on their opinion of the new evidence available.	is not relevant to our conclusions. Readers of our report can make those judgments themselves. Furthermore, as stated in our protocol, ICER relies on GRADE, an internationally accepted standard, to evaluate the quality of new evidence submitted, and we use the ICER Evidence Rating Matrix to judge the magnitude of the new benefit.
4.	Since its FDA approval in 2002, HUMIRA has helped transform care for 1,000,000+ patients who suffer from the effects of immune-mediated diseases. AbbVie's dedicated investment in HUMIRA research and development has resulted in multiple indications to serve patients living with a variety of immunological diseases including HS and has also resulted in patient-centric innovations (e.g., citrate-free HUMIRA, new dosing configurations). AbbVie has also been committed to developing and maintaining patient support programs that have been proven to help advance and improve the patient experience (e.g., AbbVie Complete, AbbVie's Patient Assistance Programs). The cumulative impact of AbbVie's decades-long investment and innovations is that HUMIRA is today a therapeutic option available to a diverse set of patients suffering from ten different immune-mediated diseases in the U.S., including pediatric diseases, and orphan or rare diseases for which patients have limited treatment options. This outcome cannot be underemphasized: at its launch in December 2006, HUMIRA was only approved to treat a single disease. Twenty years later, AbbVie's ongoing research remains committed to HUMIRA and its proven ability to help patients achieve their treatment goals. AbbVie provided evidentiary support that included recently published data evaluating the real-world use of HUMIRA and the positive impact on patients. ICER rejected each of these studies and stated they were either "published outside the timeframe of review" or "intervention/comparison not relevant to scope."	Please see GER 5a

#	Comment	Response/Integration
	AbbVie believes real-world data related to the patient experience with a product is highly relevant and needed to assess the value of therapy. As such, we disagree with ICER's assertion that such data is not relevant to their assessment.	
5.	Beyond ignoring HS, ICER ignored all other HUMIRA indications that represent less than 10 percent of HUMIRA's use. In limiting the assessment to indications representing greater than 10 percent use, ICER excluded HUMIRA's clinical and economic value in smaller patient populations, including rare conditions (i.e., HS and uveitis {non-infectious intermediate, posterior, and pan uveitis: NIIPP} juvenile idiopathic arthritis and pediatric Crohn's disease) and orphan indications (i.e., pediatric ulcerative colitis, pediatric uveitis (NIIPP), and adolescent hidradenitis suppurativa that reflect our commitment to innovation and improvement in net health benefit.4 By consistently excluding evaluation of a product's value in small patient populations with limited treatment options, ICER minimizes patients' needs and dismisses the significant benefit and value a medicine brings .	Please see GER 5a and 5b
6.	Finally, it is important to note that while drug list price (Wholesale Acquisition Cost, WAC) is well established, list prices are not what health plans and federal programs like Medicare and Medicaid ultimately pay for drugs. ICER recognizes this by including a calculation of net price impact in their analysis. The net price increase calculated by ICER (1.95%) is well below the Medical CPI, a benchmark used by ICER to determine inclusion in the report – though it is only applied by ICER to WAC price changes. If ICER compared net price increase against Medical CPI, a measure that would be more closely associated with what is paid by plan sponsors, HUMIRA would not be included in this report. Further, ICER identifies a net spending increase of $386 million. This notation by ICER is added for dramatic effect given that ICER does not identify that the net spending increase is based on the number of patients using and benefiting from HUMIRA. Products with a smaller number of utilizers have less net spend. In this respect, HUMIRA is penalized for having a breadth of indications as well as broad patient impact.	The UPI protocol was developed (and revised over time) with a multistakeholder group that includes manufacturers. Those manufacturers had particular concerns about focusing on percentage changes in net price as these can be outside the control of the manufacturer. We note that spending an additional $386 million on a therapy is likely to seem dramatic and this has little to do with any "dramatic effect" from ICER. It seems particularly important that a widely used and expensive treatment not raise its list price substantially faster than inflation.
7.	As outlined above, AbbVie believes that the totality of evidence must be evaluated as part of any value measurement. Further, AbbVie believes ICER continues to dismiss concerns that there are no recognized scientific or even ICER-defined standards to determine how much of a price increase is supported based on new clinical evidence. The result of this opaque process is an UPI report based on the opinions of ICER reviewers. We vehemently disapprove of this methodology, which is not informed by the totality of evidence that exists for a product.	As noted in other responses, ICER does not attempt to assess whether the amount of a given price increase is justified; rather, we look to see whether there is any new evidence that could be used to justify any price increase. Details of our approach in judging new evidence is well described in our UPI protocol

#	Comment	Response/Integration
	Amgen	
1.	2. **Change Prolia's rating to "supported" given new, meaningful, regulatory grade evidence on over 700,000 patients.** **Considering recent CMS initiatives and the FDA's real-world evidence (RWE) framework designed to accelerate treatment access under the 21st Century Cures Act, ICER is out of step with current acceptance and thinking on RWE**.[i,ii] ICER should adopt a more comprehensive approach that embraces the use of RWE and moreover, non-RCT data to better align with the evolving landscape.[iii,iv,v] Amgen submitted two high-quality real-world studies supporting Prolia, which ICER categorized as "low quality." The first was a comparative effectiveness analysis of claims from 22,618 Medicare Advantage and commercial patients, providing new evidence that Prolia reduced fracture risk compared to alendronate.[vi] The second was a retrospective cohort study of 542,941 Medicare patients, indicating greater persistence in Prolia vs. oral bisphosphonate users.[vii] Despite being within the timeframe and scope of ICER's review, these robust findings of real-world clinical benefits were deemed insufficient. The reasoning provided for the low rating of Kim *et al.,* 2022 was, *"the absence of specific criteria that would increase the quality of evidence."* However, researchers, regulatory bodies, and academics have embraced real-world evidence with very clear recommendations for incorporating and assessing it. There is wide recognition that properly designed RWE can mirror results from clinical trials while answering questions that randomized clinical trials cannot. In the interest of alignment with contemporary research and capturing the lived patient experience, we encourage ICER to recognize that RWE can and should be held to specific standards, which are met by our submitted studies.	Please see GER 3a, 3b. We note, additionally, that high-quality evidence demonstrating the superiority of Prolia to alendronate in reducing fracture risk, as the manufacturer claims the first study demonstrates, would be extremely important. We also note that manufacturers frequently comment that ICER judges RWE observational studies unfairly. We suggest that those concerned about ICER's conclusions review the abstract presentation of this study and make their conclusions.
3.	**Though Amgen recognizes the intention to align the evidence review period and the pricing timeframe, we encourage ICER to consider that pricing decisions reflect internally available data that may not be accessible in the public domain.** For example, results from the Curtis *et al.* study have been available to Amgen since 2022, and it would be a fundamental oversight to ignore this compelling real-world evidence of Prolia's comparative effectiveness.[viii] In a cohort of nearly half a million Medicare patients, this analysis demonstrated robust and significant reductions in the risk of hip, nonvertebral (NV), non-hip/nonvertebral (NHNV), and major osteoporotic (MOP) fractures for real-world patients on Prolia compared to alendronate. This study and the Kim *et al*. study are valuable	We feel that if a manufacturer is planning to raise prices based on new evidence, that evidence should be available to the public.

#	Comment	Response/Integration
	additions to the literature, achieving head-to-head comparisons of fracture risk reduction not previously attempted in clinical trials.[ix] Further, Curtis *et al*. is *regulatory grade* evidence that abides by FDA guidance, representing the highest possible caliber of real-world research: this may be the largest and most robust real-world study ever conducted in osteoporosis. Each of these studies provides strong evidence on their own, but combined, give exciting insights that go beyond clinical trials and head-to-head comparator information that has never been studied in trials. Accordingly, ICER's evaluation of the literature ignores a plethora of evidence addressing the knowledge gaps that clinical trials simply cannot fill.	
4.	**5. Change Nplate's rating to "supported" given the investment in and successful FDA approval of a new indication.** **ICER's decision to dismiss Nplate's new H-ARS indication as representing <10% of its potential usage is grounded in impractical uptake projections.** ICER's protocol states that it will only consider supporting evidence in an indication currently below 10% of overall use "*if manufacturers report that use is rapidly increasing*." However, ICER has failed to account for the value Nplate provides in H-ARS – an uncommon but debilitating condition. The onset of H-ARS is limited to circumstantial radiation exposure, requiring the proactive development of novel therapeutics before catastrophic events occur. Contrary to most disease areas where treatments are developed in response to data demonstrating unmet need, Nplate's value in treating H-ARS cannot be adequately assessed without special consideration surrounding the unique manifestation of this condition. To move science forward and simultaneously protect the needs of rare disease patients under the Orphan Drug Act, it is important that indications are neither discounted nor prioritized according to the number of patients that suffer from that disease. *[Comment continues on the next page]*	We acknowledge that it is valuable to have treatments "on the shelf" that can be used in case of a future need. Valuation and pricing for antibiotics and some vaccines are examples of this special case. However, we do not believe that a price increase for all current uses of Nplate is merited given that it does have active uses in the commercial market and any special arrangement for increasing the price as part of a program to stockpile the drug or to take other special measures to safeguard use of this treatment in case of a national emergency should be negotiated separately with the government.

#	Comment	Response/Integration
	ICER fails to consider Nplate's unique applications and its role in U.S. national security. It should be noted that H-ARS is an incredibly specific indication associated with intense radiation exposure from atomic bombings, nuclear powerplants, and sterilization radiators.[x] An indication that cannot be ethically tested in humans is unlikely to, and hopefully will *never,* comprise more than 10% of use. It is important that innovation in these rare conditions not be undermined simply because of the timing of approval vs. use, particularly for products like Nplate that could one day be critical to national security and public health. As exhibited by the fallout of the COVID-19 pandemic, preparation for these unforeseen national emergencies can save countless lives and incalculable long-term costs.	
6.	**The exclusion of Nplate's FDA-approved label based solely on it being categorized as a *"study protocol/editorial/conference citation with no abstract"* appears to be a very literal interpretation of ICER's criteria and raises questions regarding the validity of ICER's approach.** Amgen provided Nplate's FDA prescribing information as the foundational evidence supporting the approval of a new indication within ICER's timeframe. As with all FDA labels, it captures every relevant clinical study and explicates how these data demonstrate net benefit and qualify the drug's suitability for real-world use. The downgrading of an FDA label – representing the ultimate benchmark of efficacy, safety, and regulatory acceptance – suggests ICER is putting its own criteria ahead of the FDA's.	The rationale for excluding this has now been revised. Since the label was submitted for the H-ARS indication, it was excluded because we do not believe that the indication of H-ARS accounts for at least 10% of the overall utilization of romiplostim.
7.	**Compelling new evidence in recent years has demonstrated Prolia and Nplate's clinical and real-world value.** High-quality claims data have offered head-to-head evidence of Prolia's advantages over alendronate, while extensive studies in Nplate led to a new FDA-approval in H-ARS that enhances national security and preparation for "never events." ICER should keep pace with regulatory, disease, and scientific communities' broad and expanding embrace of real-world evidence and apply the established standards for assessing its quality, rather than discounting non-RCTs entirely. ICER must also reconsider the validity of its protocol restrictions and review its criteria to avoid disregarding the importance of label expansions into rare diseases or excluding universally endorsed sources like FDA prescribing information. Amgen stands behind the value of its products and maintains a commitment to serving patients through innovation, responsible pricing, and excellence in research.	We do not discount non-RCT studies. Please see GER 2a, 3a, 3b, and 5a.
	Bausch Health	

#	Comment	Response/Integration
1.	Bausch would like to acknowledge that for the 2023 Manufacturer Input Response Phase II, ICER's search identified 19 articles of which 0 were screened as full text. The full text articles associated with these 19 articles may contain valuable information in the manuscript body but not reported in the abstract. We would like to note that the Abdel Moneim M, 2021,2 study screened by ICER is an open-label parallel, prospective interventional study, assessing outcomes of 400 mg rifaximin 3 times daily plus lactulose 3 times daily compared to lactulose alone amongst HE patients with Hepatitis C virus-related cirrhosis. This study showed that the resistance to rifaximin (measured as difference in minimum inhibitory concentration of rifaximin of intervention vs control) was not significantly different amongst those in the rifaximin group (vs lactulose alone). However, the authors reported that those in the rifaximin group had significantly lower risk of developing HE and the time to first episode of HE event was longer. Further, the authors also found that none of the rifaximin-associated adverse effects were life-threatening or required hospitalization over the 6-month study period. Another study that ICER screened is the study by Zeng X, 2021,3 a multi-center open label prospective study, which assessed the outcomes of low dose rifaximin 400 mg twice daily for 6 months compared to conventional therapy in patients with decompensated liver cirrhosis. This study showed that low dose rifaximin reduced overall complications, had no significantly different effect on transplantation-free survival, but markedly reduced the episodes of ascites exacerbation, HE and gastric variceal bleeding. While the dose used in these studies (i.e. 400 mg rifaximin 3 times daily [Abdel Moneim M]; 400 mg twice daily [Zeng X]) and the on label study population does not conform to the FDA-approved XIFAXAN label for HE, the studies do show rifaximin's value in terms of lowering the risk of development of an HE episode and time to HE episode in line with the FDA label.	We do not believe that the study population in Abdel Moneim M et al. 2021 accounts for at least 10% of the overall utilization of rifaxamin. Zeng X, 2021 was also excluded because the study population was outside of the approved label indication for rifaxamin. Please see GER 5a and 5b.
2.	We would like to highlight a few important studies published within the 2023 ICER UPI review period (i.e., January 2021 – December 2022) that highlights evidence supporting the value of XIFAXAN. The Volk ML, 2021,4 study is a real-world evidence study that highlights the reduction in healthcare utilization (HE-related and all cause IP admissions and days) and costs associated with the use of and adherence to rifaximin (vs lactulose alone) amongst commercially insured patients with HE using Marketscan Commercial claims and Optum Clinformatics Data Mart databases. When considering the study results in a simulated plan of 1 million lives, if payors and physician ensured adherence to rifaximin, the total cost savings would be $5.9 million per year ($0.49 per-member-per-month [PMPM]) using	This is a newly submitted reference. Therefore, we will not be reviewing it as it is long past the deadline stated in the UPI Protocol for evidence submission and evaluation.

#	Comment	Response/Integration
	results from Marketscan and $4.4 million per year ($0.37 PMPM) using results from Optum. Additionally, if 50% of patients with HE who were treated with lactulose alone had rifaximin added on and were adherent to their rifaximin therapy, the total cost savings would be-- $7.5 million per year or about $0.62 PMPM (Marketscan); $6.1 million per year or $0.50 PMPM (Optum). The Volk ML, 2021 study findings have been central to payor interactions and have enabled several payers to make key decisions on XIFAXAN coverage.	
3.	A single-center retrospective cohort analysis by Chang C, 2021,5 compared the long-term efficacy (1-year) of rifaximin add-on to lactulose versus lactulose alone among adults with at least 2 episodes of HE. Outcomes assessed were time to first HE recurrence (Conn score ≥ 2), numbers and days of hospitalization attributed to HE and certain laboratory/clinical parameters (e.g., serum ammonia level, Mini-mental state examination, etc.) Patients treated with rifaximin + lactulose vs lactulose alone had a significantly longer median time (204.50 days vs. 125.00 days; p = 0.044) to first HE recurrence (Conn score ≥ 2) and significantly lower odds (odds ratio: 0.214 [p = 0.045]) of experiencing HE recurrence. Treatment with rifaximin + lactulose (vs lactulose alone) led to a lower number of HE hospitalizations (median 1 vs. 3; p < 0.001] and days of HE hospitalization [median 11 vs. 37; p = 0.003].	This is a newly submitted reference. Therefore, we will not be reviewing it as it is long past the deadline stated in the UPI Protocol for evidence submission and evaluation.
4.	Hudson M, 2021,6 in a retrospective observational extension study assessed the long-term survival (5-year) in HE patients receiving rifaximin-α treatment. The median (interquartile range) survival was 2.8 (0.8–5.0) years with 1-, 3-, and 5-years survival rate following rifaximin-α treatment of 72%, 49% and 35%, respectively. Approximately one third of patients (35%) on rifaximin-α survived after 5 years which compared favorably with 15% survival at 5 years reported in similar patients not receiving rifaximin-α (Jepsen P, 20107).	This is a newly submitted reference. Therefore, we will not be reviewing it as it is long past the deadline stated in the UPI Protocol for evidence submission and evaluation.
5.	We would further like to highlight key real-world evidence studies published in 2023 supporting the value of XIFAXAN, that have been critical for payor interactions.8-11 Jesudian AB, 2023,8 assessed the impact of rifaximin (± lactulose) use following discharge of an initial overt hepatic encephalopathy (OHE) hospitalization on OHE rehospitalizations and healthcare costs among commercially insured OHE patients. The study results highlight that those treated with rifaximin (vs. no rifaximin treatment) following discharge from initial OHE hospitalization had a significantly lower 30-day risk of experiencing OHE rehospitalization (44% lower) and a significantly lower annual rate of OHE hospitalizations (59% lower). Further, when the study cohorts were stratified into four subgroups representing decreasing quality of care (QoC; Type 1:	This is a newly submitted reference. Therefore, we will not be reviewing it as it is long past the deadline stated in the UPI Protocol for evidence submission and evaluation.

#	Comment	Response/Integration
	Received rifaximin without any time gap following the index OHE hospitalization; Type 2: Received rifaximin within 30 days post-discharge; Type 3: Received lactulose within 30 days post-discharge; Type 4: Received no rifaximin/lactulose within 30 days post-discharge), results showed that decreasing QoC (type 1 to type 4) was associated with a higher risk of 30-day rehospitalization and higher annual rates of hospitalization. Finally, reduced medical costs in the rifaximin treatment cohort offset the increased pharmacy costs, resulting in no significant total cost differences observed between the rifaximin treated vs not treated cohort. Findings from this study highlight the importance of treating patients with rifaximin immediately following an OHE hospitalization to reduce the risk of future OHE hospitalizations and economic burden.	
6.	A study by Wong R, 2023,9 assessed the trends of cirrhosis prevalence, OHE prevalence, OHE hospitalizations and costs, and XIFAXAN use and costs from 2006-2020 among a commercially insured population. Findings from this study show that the prevalence of cirrhosis and OHE increased by 5.2% year over year (YOY) and 4.4% YOY, respectively. Further, the rates of OHE hospitalization using various definitions decreased from 32.3%-56.0% to 5.5%-28.4% (2006 to 2020). Utilization of XIFAXAN increased from 2.2% in 2010 (XIFAXAN for HE approved in 2010) to 6.3% in 2020. Of note, the cost of OHE hospitalization increased by 4.5% YOY from 2010-2020 ($39,333 to $77,699) and especially a marked increase ($38,193 to $77,699) from 2015-2020 (8.1% YOY). During the 2015-2020 period, though monthly XIFAXAN cost increased from $1,811 to $2,389, the YOY increase of 4.5% was lower than the YOY increase of costs of OHE hospitalizations during the same period. The findings of this study highlight that the prevalence of cirrhosis and OHE over time increased; rates of OHE hospitalizations decreased but the cost of OHE hospitalization increased; the YOY increase in cost of XIFAXAN was lower than the YOY cost increase of OHE hospitalization.	This is a newly submitted reference. Therefore, we will not be reviewing it as it is long past the deadline stated in the UPI Protocol for evidence submission and evaluation.
7.	Jesudian AB, 2023,10 assessed the impact of gaps in XIFAXAN access due to prescription claim rejections on OHE hospitalizations and costs. This study highlights that rejection-related gaps in access to XIFAXAN were associated with a significantly higher risk (incidence rate ratio of 1.55-3.19) of experiencing OHE hospitalization compared to no rejection related gaps of XIFAXAN, with the risk of OHE hospitalization increasing with the length of access gap (≥7 to ≥ 21 days). Further, longer length of rejection-related access gaps was associated with higher total medical costs ($1,579-$3,413 PMPM) compared to no rejection related gaps. Findings from this study highlight the importance of having continuous access	This is a newly submitted reference. Therefore, we will not be reviewing it as it is long past the deadline stated in the UPI Protocol for evidence submission and evaluation.

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	to XIFAXAN to reduce the risk of OHE hospitalization and increased healthcare costs.	
8.	Of importance, there was no OHE-specific *International Classification of Diseases, Tenth Revision (ICD-10)* code from October 1, 2015, to September 30, 2022, which may have led to an underestimation of the burden of OHE. Jesudian AB, 2023,11 using in-hospital database (October 1, 2015-June 30, 2022) developed an algorithm to identify an active OHE hospitalization event. Hospitalizations with ≥1 dose of in-hospital rifaximin or lactulose, and ≥1 ICD-10 code for altered mental status, unspecified encephalopathy, and/or cirrhosis or its complications (i.e., varices, hepatorenal syndrome, spontaneous bacterial peritonitis) were identified as an active OHE hospitalization event. Hospitalizations identified using this criterion for OHE hospitalization on average had 2.0X longer length of stay and 2.5X times higher hospitalization billing charges compared to hospitalizations identified based solely on a primary diagnosis of OHE (OHE hospitalization defined using Centers for Medicare & Medicaid Services General Equivalence Mappings). Findings from this study highlight that the burden of OHE (rate, length of stay, and associated costs) has been likely underestimated, which may further highlight the importance of XIFAXAN for reducing the healthcare burden associated with OHE.	This is a newly submitted reference. Therefore, we will not be reviewing it as it is long past the deadline stated in the UPI Protocol for evidence submission and evaluation.
9.	We strongly believe that the recent published evidence further underscores and enhances the value of XIFAXAN for HE. However, dismissing key pieces of recent and relevant evidence due to a restrictive evidence review period and search strategy trivializes this valuable evidence. This pattern of overlooking recent evidence potentially diminishes the submitted evidence and its value for making informed decisions by key stakeholders. In conclusion, we continue to disagree with ICER's UPI assessment protocol and how it continues to dismiss the multiple recent and relevant studies which provides US payors and patients relevant insights into the true value of XIFAXANs yet are likely to be categorized as "outside of the time frame".	This is a newly submitted reference. Therefore, we will not be reviewing it as it is long past the deadline stated in the UPI Protocol for evidence submission and evaluation.
	Genentech	
1.	**Change the conclusion for Perjeta to be *supported by new clinical evidence* given the recognized impact of this practice changing data in the medical community.** As outlined in the data submitted to ICER, five clinical studies were published between January 2021 and December 2022 highlighting Perjeta's efficacy in diverse contexts. These findings collectively expanded our understanding of pertuzumab's therapeutic potential across various clinical scenarios (see Table 1 below) and resulted in practice changing recommendations by the National Comprehensive Cancer Network® (NCCN®). Earlier this	We evaluated both the APHINITY and PATRICIA trials. Please see our responses to comments 2 and 4 below for why we did not consider these trials as providing new clinical evidence under the UPI protocol.

#	Comment	Response/Integration
	year, the NCCN revised their eBC guidelines, elevating pertuzumab/trastuzumab to a Category 1 preferred recommendation for HER2-positive, node-positive patients, irrespective of hormone receptor (HR) status [1]. Moreover, the NCCN also recommended the inclusion of pertuzumab and trastuzumab as a treatment option for brain metastases in patients with HER-2 positive breast cancer (category 2A) in 2022 [1]. Both recommendations were based on the latest APHINITY and PATRICIA trials, which we submitted to ICER but they declined to include in their assessment.	
2.	Loibl et al 2022 [2]: New evidence confirms long-term efficacy of pertuzumab in eBC patients with a high risk of recurrence. The APHINITY trial has had a significant impact on clinical practice. With 8.4 years of median follow-up, it has presented compelling evidence that pertuzumab's benefit in HER2+ eBC endures, with the greatest advantages seen in the N+ cohort, irrespective of HR status. Results from the updated trial prompted NCCN to elevate the combination of pertuzumab and trastuzumab to Category 1 status for this population, playing a pivotal role in shaping treatment strategies for high-risk eBC patients [1].	We don't disagree that the findings from the APHINITY trial have had a significant impact on clinical practice. However, the primary findings from the APHINITY trial were published in 2017 (outside of the time frame for this review). The findings in the longer-term follow-up presented by Loibl et al. (no statistically significant difference in overall survival in patients on pertuzumab; improvement in the rates of invasive-disease-free survival among patients with HER2-positive, early breast cancer was maintained) were similar to what was observed in the primary publication. Given the prior belief about the long-term benefit of this therapy, under the UPI protocol, we do not consider the information from Loibl et al. new clinical evidence to support a price increase. Please See GER 1a and 1b.
3.	Swain et al 2022 [3]: New evidence reinforces the clinical benefits of pertuzumab in eBC neoadjuvant to adjuvant treatment continuation. Evidence from the pooled analysis suggests that pertuzumab, in combination with trastuzumab, provides the most clinical benefit, when included in both neoadjuvant and adjuvant setting among patients with HER2+ eBC who have a pathological complete response after neoadjuvant HER2-targeted therapy plus chemotherapy. The results reinforce the clinical benefits of pertuzumab in eBC.	Swain et al. is a pooled analysis of five trials published before the time frame of this review. The findings from this study are consistent with many of the individual studies and other previously published pooled analyses cited by the authors. As such, we believe Swain et al. provide previously known information about pertuzumab.
4.	Lin et al 2021 [4]: New evidence supports the efficacy of pertuzumab in central nervous system (CNS) metastases, a population with high unmet need. Based on the evidence from the Phase II PATRICIA trial, and a non-pre-specified exploratory analysis of the pivotal Phase 3 CLEOPATRA, pertuzumab, in combination with trastuzumab, is now guideline recommended as a viable option for treating brain metastases in previously untreated HER2+ mBC [5].	Lin et al. 2021 (PATRICIA trial) was a small, single-arm trial that provided only low-quality evidence on the CNS benefit of pertuzumab plus high-dose trastuzumab. Furthermore, although the trial provides data showing that pertuzumab plus high-dose trastuzumab may have benefits in patients with CNS metastasis, it does not provide evidence that adding pertuzumab to high-dose trastuzumab provides additional benefits versus high-dose trastuzumab

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		alone. Under the UPI Protocol, we do not assess the magnitude of benefit in the absence of moderate or high-quality evidence CLEOPATRA trial is a newly submitted reference. Therefore, we will not be reviewing it as it is long past the deadline stated in the UPI Protocol for evidence submission and evaluation.
5.	Yamamoto et al 2022 [6]: New evidence supports the efficacy of pertuzumab retreatment in later treatment lines. The PRECIOUS study revealed that retreatment involving pertuzumab, trastuzumab, and chemotherapy in advanced HER2+ breast cancer patients, who had received prior pertuzumab-containing regimens, led to a notable improvement in progression-free survival (PFS). These results provide evidence for the potential efficacious effect of dual HER2 blockade with pertuzumab as an additional treatment choice in later lines of therapy for these patients.	Pertuzumab is used in combination with trastuzumab and chemotherapy for the treatment of patients with HER2+ breast cancer (MBC) who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. Yamamoto et al 2022 (PRECIOUS study) was conducted in a population outside of the approved indication of pertuzumab as it evaluated re-treatment with pertuzumab in patients who have previously been treated with pertuzumab. While this study demonstrates a potential use of pertuzumab in that population, we do not believe it justifies increasing the price of pertuzumab before it is approved for use in that population.
6.	Takahashi et al 2021 [7]: New evidence supports the efficacy of pertuzumab in Japanese patients who previously did not show benefits in the CLEOPATRA trial. The COMACHI study confirmed that the combination of pertuzumab plus trastuzumab and docetaxel is efficacious and well-tolerated in Japanese patients with HER2+ recurrent or mBC, hence providing patients with more efficacious treatment.	Takahashi et al 2021 (COMACHI study) was excluded because it is outside the scope of this review. It is a single-arm study conducted to confirm the efficacy of pertuzumab plus trastuzumab and docetaxel in Japanese patients. While this is an important study, we do not believe it justifies increasing the price of the treatment in US.
7.	**In alignment with ICER's own approach to value assessment, consider evidence beyond randomized clinical trial data that demonstrates the impacts of Perjeta on patients and their families, the healthcare system and society overall.** ICER's decision to dismiss the clinical evidence we provided is disappointing. For example, ICER opted not to evaluate the extent of benefits in cases where evidence is available from phase II clinical trials. This decision was made despite the inherent challenges of conducting phase III clinical trials, as in the case of the PATRICIA study that evaluated the effect of Perjeta among patients with HER2+ mBC with CNS metastases [4]. It is worth noting that HER2Climb was also a Phase II trial yet the FDA approved label for CNS mets. And both PATRICIA and HER2Climb studies received NCCN CNS listings [5]. For years, patients with breast cancer and brain metastases were typically excluded from clinical trials due to the prevailing belief that anticancer drugs couldn't effectively penetrate the blood-brain barrier [8]. The PATRICIA study, however, emerged as one of	It is incorrect that we do not evaluate Phase 2 clinical trials. Based on our UPI protocol, we rate the magnitude of the benefit of any new evidence that is rated as being of moderate or high quality. Please see the response to comment 4 above for our rationale for excluding the PATRICIA Phase 2 trial.

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	the first studies to provide compelling evidence that systematic targeted therapies can indeed benefit patients facing these substantial unmet medical needs. The results of the PATRICIA study, along with other clinical evidence, led to the NCCN panel uniformly recommending the inclusion of pertuzumab and trastuzumab as a viable option for patients with HER2+ breast cancer and brain metastases, receiving a category 2A recommendation in 2022 [5]. This underscores a significant disconnect between ICER's perspective on what constitutes reliable evidence versus the medical community dedicated to the care of these patients. Similarly, ICER decided to dismiss clinical evidence supporting retreatment of patients with advanced stages of their cancer, another high unmet population.	
8.	The value of Perjeta extends beyond the scope of the studies that ICER are willing to review in their UPI report. While their assessments have been confined to specific clinical trials and data within a limited arbitrary timeframe, it's crucial to recognize that new and evolving evidence continues to emerge, offering a more comprehensive perspective on Perjeta's impact. A prime example of this is a recent model that translates individual outcomes into projected population benefits of Perjeta in preventing recurrence among a substantial cohort of HER2+ eBC patients. According to this model, the use of Perjeta in both neoadjuvant and adjuvant settings is projected to prevent 20,596 recurrences between 2013 and 2031, resulting in over $8.5 billion in healthcare cost savings during the same period [9,10]. This projection underscores the substantial and long-lasting positive effects that Perjeta can have on both the patients and the US healthcare system.	Thank you for providing this context.
9.	**Finally, we recommend that ICER either revise methods or discontinue the UPI report given that its flawed methodology presents an unbalanced and narrow picture of both drug value and investment in clinical research.** Year over year, ICER receives consistent criticism about how the UPI report draws connections between pricing trends and evidence [11-13]. In particular, ICER makes conclusions on whether prices are *supported/unsupported* based on clinical trial data published in an arbitrary two-year period preceding price changes. New evidence on the impact of treatments grows and proliferates over time based on new research questions learned through real world use of a medicine. ICER's decision to consider only the preceding two years of new evidence has no basis and it fails to appropriately value the significant ongoing investment in research for new indications, new delivery mechanisms, and other manufacturer-funded health system interventions that	The UPI protocol was developed (and revised over time) with a multistakeholder group that includes manufacturers.

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	aim to improve patient outcomes and experiences. Further, ICER's current methods place almost a sole emphasis on randomized clinical data via use of the GRADE criteria and its narrow consideration of other forms of evidence. This approach fails to recognize that non-randomized trials may be the only suitable, ethical option to explore some outcomes and that real world data plays a vitally important role in exploring a broader range of clinical, economic and humanistic outcomes under routine care [14]. Many of the important ways treatments impact patients and their families and the healthcare system cannot be studied adequately in clinical trials alone.	
10.	ICER has stated that its goal as an organization is to *"provide the public and policymakers with information they can use to advance the public debate on drug price increases"* [11]. The methods used to assess whether a price increase is *supported* in the UPI report stand in stark contrast with ICER's approach to its core work on value assessment. As outlined in its newly updated value assessment framework, ICER clearly supports that decisions on treatments should include broader impacts beyond what is studied in clinical trials [15]. Information on price should be shared alongside balanced information on treatment's disease-related impacts across patients and other stakeholders, including information on quality of life, adherence, family spillover effects, unmet need, and others. The annual UPI report has failed to evolve alongside ICER's other activities. As it stands, the UPI report presents an unbalanced and narrow picture of investment in clinical research that cannot support informed debate on drug prices. It is time for ICER to reconsider whether the UPI report truly supports its goals.	Under the UPI Protocol, manufacturers are welcome to provide information outside of new clinical evidence that they feel justifies price increases. ICER will not alter its rating based on this evidence but will publish the manufacturers justification in the UPI Report. We highlight that the full version of the quote in the comment says: *It is important to note that ICER does not currently have the capacity to perform full economic analyses on the therapies evaluated in this report, nor would the time needed to develop full ICER reports (at least eight months) provide information in a useful timeframe for the public and policymakers. Therefore, this UPI report is not intended to determine whether a price increase for a drug is fully justified by new clinical evidence or meets an ICER health-benefit price benchmark. Instead, the analyses focused on whether substantial new evidence existed that could justify a price increase. By identifying whether there is, or is not, new evidence of improved safety or effectiveness for drugs with substantial price increases, we hope to take an important first step in providing the public and policymakers with information they can use to advance the public debate on drug price increases.*
Incyte		
1.	Given Incyte's commitment to patients and ongoing investment in research and development, we agree with ICER's recognition that the value of Jakafi is clearly supported by new clinical evidence. Jakafi is an oral Janus-associated kinase 1 and 2 (JAK1/JAK2) inhibitor with a proven clinical and safety profile with over 10 years of experience. Jakafi is the only FDA-approved treatment across the orphan indications[1] of:	To clarify, the UPI analysis does not examine whether the price for Jakafi is justified. This would require a full cost-effectiveness analysis, which was not performed. The UPI Report concluded that there was moderate-quality evidence of a benefit with Jakafi that was not previously known. Thus, Jakafi had a price increase with new evidence.

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	• Myelofibrosis (MF): intermediate or high-risk MF, including primary MF, post-polycythemia vera MF and post-essential thrombocythemia MF in adults (approved November 16, 2011); • Polycythemia Vera (PV): in adults who have had an inadequate response to or are intolerant of hydroxyurea (approved December 4, 2014); • Graft-Versus-Host Disease (GVHD): o steroid-refractory acute GVHD in adult and pediatric patients 12 years and older (approved May 24, 2019); o chronic GVHD after failure of one or two lines of systemic therapy in adult and pediatric patients 12 years and older (approved September 22, 2021).	
2.	Since Jakafi was first approved, Incyte has continued to invest in developing evidence to better understand the real-world value Jakafi brings to patients and to discover the potential of Jakafi for additional patient populations with high unmet need. Incyte agrees with ICER's determination that MAJIC-PV and REACH3 are trials of good quality that demonstrate "substantial benefit for ruxolitinib," reinforcing ICER's conclusion that Jakafi's pricing was supported during the timeframe of ICER's review.[2,3,4] MAJIC-PV was the first study to demonstrate a correlation between attaining a complete response and event-free survival in patients with hydroxyurea-resistant or intolerant PV. Additionally, this study demonstrated the relationship between ruxolitinib therapy and improved thrombosis-free survival and event-free survival in a long-term prospective study. The REACH3 evidence led to a new FDA-approved indication in chronic GVHD and a Category 1 upgrade in the National Comprehensive Cancer Network (NCCN) guidelines, which represents the highest level of evidence available supported by uniform consensus of experts that the treatment intervention is appropriate.	Thank you for providing this context.
3.	Incyte is driven by rigorous science and our pricing decisions allow us to invest in scientific advancements in areas of high unmet medical need. In 2021 and 2022, Incyte invested nearly $1.5B and $1.6B in research and development, representing 49% and 47% of the company's total net revenues, respectively. These research and development costs include investment as part of our ongoing LIMBER (Leadership In MPNs Beyond Ruxolitinib) clinical development initiative. LIMBER is designed	Incyte's investments in research and development are helpful context in concert with the price increase data presented within this Report on Jakafi.

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	to improve and expand therapeutic options for patients with myeloproliferative neoplasms and includes the evaluation of combinations of Jakafi with other therapeutic modalities.	
	Pfizer	
1.	**The net price increase of 4.45% taken for IBRANCE during the reference period is a fair reflection of the value IBRANCE brings.** Pfizer appreciates ICER's acceptance of the corrected 4.45% net price increase calculation. Pfizer is committed to ensuring that the price of medicines is a fair reflection of the value they bring and has adjusted the net price in reaction to inflationary pressure. As a comparison, US prices for medical care rose 4% from December 2021 to December 2022.[39] As such, we question whether IBRANCE remains in the top 15 drugs whose net prices have had the largest impact on US spending in that timeframe after having provided the net price percentage correction. Pfizer's purpose is to create breakthroughs that change patients' lives, with affordability being a critical factor. Pfizer remains dedicated to improving access and affordability for patients who rely on our medications and work with an array of healthcare stakeholders to develop sustainable solutions addressing these issues, including a potential reform to the current US healthcare system. Pfizer has taken a proactive approach to address this challenge in multiple ways. For example, Pfizer provides discounts, rebates, and other fees to insurers, pharmacy benefit managers, federal government programs, and other key stakeholders in the healthcare ecosystem to ensure that our medicines are accessible and affordable to the patients who need them. Pfizer also provides patient support through multiple sources, such as a patient assistance program and numerous partnerships with cancer-related patient advocacy groups.	ICER adhered to our research protocol in determining whether Ibrance should be included in our 2023 UPI assessment; details of the selection process are provided in the full report and appendices.
2.	**RWE complements findings from RCTs and yields pertinent new information for clinical decision making.** Pfizer appreciates that contrary to previous years, ICER seems to place a greater weight on RWE studies. We appreciate this as Pfizer has made considerable efforts to ensure that RWE studies are well designed, appropriately powered, and use reliable, valid, and fit-for-purpose data. However, we question the assertion that the submitted RWE studies do not provide relevant new information (two examples are provided below). This classification was presented without any explanation on why and thus lacks transparency.	Please see GER 2a and 2b.

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	Pfizer believes that though RCTs are the gold standard in determining the safety and efficacy of a drug in a controlled setting, RWE informs clinical decision-making, and when combined with RCTs depict a more complete picture of a therapy.[40] While treatment randomization decreases risk of bias and confounding in an RCT, patient populations are selected using strict eligibility criteria and are required to strictly adhere to treatment protocols that often do not reflect the typical patient mix and treatment procedures seen in clinical practice.[41] RWE may therefore provide both new and complementary treatment effectiveness and safety results for the overall patient population, including patients often underrepresented or absent in RCTs. For instance, OS represents a key outcome in cancer trials. However, in metastatic breast cancer, where patient survival is much longer than other tumor types, progression-free survival (PFS) is the typical primary endpoint, with OS as secondary due to OS results not being available for many years and the potential impact of multiple treatments post progression. This lag in OS results can sometimes be addressed by RWE, where real-world data are potentially available before large phase III clinical trials results. This was the case with IBRANCE, where rapid uptake post approval led to an availability of real-world OS data before final readout from the phase III RCT, PALOMA-2. Therefore, well-designed RWE has the potential to provide important new evidence that can complement RCTs.	
3.	Pfizer considers that all the provided RWE studies contain "new information on the efficacy or safety" of IBRANCE as they are focused on populations reflecting real-world US clinical practice and including subgroups often underrepresented in clinical trials, e.g., elderly patients, African American patients, and patients with select metastases.	Please see GER 1a and 1b.
4.	Pfizer would like to highlight two of the well-designed RWE studies that provided new information on the effectiveness of IBRANCE at the time of publication. Both studies compared the efficacy of palbociclib plus aromatase inhibitor (AI) compared with AI monotherapy using validated survival endpoints from the Flatiron Electronic Health Records dataset, a national database accounting for over 800 sites of care across the US.[42] The first study we would like to highlight is DeMichele et al, 2021.[43] DeMichele et al, 2021, found that after adjusting for imbalances in baseline demographics and clinical characteristics using propensity score-based methods, US patients receiving palbociclib with letrozole (N=772) compared with letrozole alone (N= 658) in the first-line setting had a statistically	We have re-evaluated this and agree that we should not have excluded DeMichele et al. 2021 as previously known information. We have now reviewed the study. Although this is a high-quality observational study, we consider it to provide low-quality evidence on overall survival benefit for patients. This study is now summarized in our main report.

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	significant 42% reduction in risk of disease progression and 34% reduction in risk of death. [43] At the time of this publication, the only OS data available from RCTs on IBRANCE for patients receiving treatment in the first line was from the PALOMA-1 study, which was a small phase II study (68 patients receiving palbociclib and letrozole, and 81 patients receiving placebo and letrozole).[44] Additionally, the primary endpoint was PFS. Lastly, OS was a secondary endpoint, and the study was not powered to show a difference in OS. Clearly the RWE study by DeMichele et al, based on a large sample size, provided new, relevant, and important information regarding IBRANCE's comparative effectiveness with respect to OS in the US.	
5.	The second study we would like to highlight is Rugo et al, 2022.[45,46] Rugo et al, 2022, found that after a similar adjustment method, 1,342 patients receiving palbociclib with AI versus 1,564 patients receiving AI alone in the first line-setting had a statistically significant 24% reduction in the risk of death and 30% reduction in risk of progression.[45,46] At the time this publication was presented at the European Society for Medical Oncology Breast Cancer conference in May 2022, the only OS data available on IBRANCE for this indication was from the PALOMA-1 study. The primary endpoint in Rugo et al, 2022 was OS and was powered accordingly, while the secondary endpoint was real-world PFS. Additionally, this study is more reflective of US clinical practice as the patient population was broadened to include patients receiving any AI.	We have re-evaluated this and agree that we should not have excluded Rugo et al. 2021 as previously known information. We have now reviewed the study. Although this is a high-quality observational study, we consider it to provide low-quality evidence on overall survival benefit for patients.
6.	**Increasing the certainty of RCT findings yields new information that is important for patient and clinician decision-making.** Pfizer is committed to understanding the value of IBRANCE with long-term use as the certainty of outcomes are reinforced. For instance, Pfizer provided long-term pooled safety analysis from RCTs of palbociclib with endocrine therapy versus placebo with endocrine therapy.[47] As the first CDK 4/6 inhibitor approved, there was no previously known information on long-term safety signals for this drug class until this study. Therefore, such analyses support patient-physician clinical decision-making.	Please see GER 1a and 1b
7.	**Pfizer believes that the indirect comparison study on patient-reported outcomes is of high quality.** At Pfizer, we believe that every patient deserves to be seen, heard, and treated as an individual with respect and care. Patient-reported outcomes help Pfizer understand how it can improve its therapies to better serve our patients. As such, we	Thank you for your willingness to provide additional details on the protocol. However, we believe that research protocols should not only have been written in advance of the analysis, but also should have been made publicly available to ensure full transparency on

#	Comment	Response/Integration
	submitted a matching adjusted indirect comparison (MAIC) assessing the relative impact of IBRANCE with fulvestrant and abemaciclib with fulvestrant on patient reported quality of life.[48] ICER has deemed this a low-quality study, with which Pfizer respectfully disagrees. The methodology used for the study is the gold standard for indirect treatment comparisons because the design adjusts for differences in patient baseline characteristics.[49] The authors also provided strong justification for the selected effect modifiers. Additionally, the authors viewed the EORTC QLQ-C30 and EORTC QLQ-BR23 as two distinct constructs, thereby supporting their selected method to adjust for multiplicity. To address ICER's concerns on risk of bias without clear prior protocol, Pfizer creates protocols for all real-world and comparison studies. While protocols for indirect comparisons are not routinely disclosed as is required for RCTs and observational studies, Pfizer is happy to provide this protocol to ICER to review if requested.	the research approach and prevent selective reporting of outcomes. Specifically on this MAIC study, we have substantial concerns about the analysis and feel that the certainty in the estimates is low after considering issues including risk of bias without clear prior protocol for performing the MAIC; Bonferroni adjustment applied based on elements of individual scales rather than across total number of comparisons performed; concern that adjustment will not adequately control for differences in quality of life reporting characteristics across varying populations.

[i] CMS. Medicare Drug Price Negotiation Program: Initial Memorandum, Implementation of Sections 1191-1198 of the Social Security Act for Initial Price Applicability Year 2026, and Solicitations of Comments. CMS.15 March 2023. Link
[ii] US Food & Drug Administration (FDA). Real-World Evidence. FDA. 2023. Link
[iii] *ibid.* 24.
[iv] US Food & Drug Administration (FDA). Advancing Real-World Evidence Program. FDA. 2022. Link
[v] *Op cit.* CMS. 2023. Link
[vi] *Op cit.* Kim *et al.* 2022. Link
[vii] *Op cit.* Singer *et al.* 2021. Link
[viii] *Op cit.* Curtis *et al*. 2023. Link
[ix] Lyu H, Jundi B, Xu C, Tedeschi SK, Yoshida K, Zhao S, Nigwekar SU, Leder BZ, Solomon DH. Comparison of Denosumab and Bisphosphonates in Patients With Osteoporosis: A Meta-Analysis of Randomized Controlled Trials. *J Clin Endocrinol Metab*. 2019;104(5):1753-1765. Link.
[x] Centers for Disease Control and Prevention (CDC) Acute Radiation Syndrome: A Fact Sheet for Clinicians. CDC. 4 Apr 2018. Link

Appendix O. Manufacturer Comments

Full-text manufacturer comments are provided on the following pages.

Unsupported Price Increase Report
2023 Assessment

AbbVie Response to HUMIRA Assessment

October 24, 2023

AbbVie supports an evidence-based value assessment paradigm that reflects the unique and diverse criteria of stakeholders impacted by the assessment and those making healthcare decisions, and that preserves shared decision making between patients and their healthcare providers. AbbVie welcomes the opportunity to comment on ICER's Preliminary Unsupported Price Increase (UPI) assessments of HUMIRA.

ABBVIE'S POSITION ON ICER UNSUPPORTED PRICE INCREASE ASSESSMENT

AbbVie contends that the methodology and purpose of this assessment remains flawed. With intrinsic limitations of evaluating evidence, uncertainty of net price, and incomplete measurements of value, ICER's UPI report could inappropriately impact patient access to medicines and lead to oversimplified pricing policies, and value assessment decisions.

AbbVie believes that ICER's UPI analysis is subjective. ICER does not set any specific parameters in their methodology for exactly what new clinical evidence would support a price increase of a certain magnitude, nor are there industry standards for doing so. Additionally, we believe ICER utilizes an opaque and inconsistent process to determine whether sufficient clinical evidence exists to support price increases. Given this lack of scientific rigor, we maintain that ICER's findings in the UPI report are merely ICER's opinion and should not be used to determine access to treatment or to inform policy decisions.

AbbVie believes that the determination of value demands a comprehensive scientific approach encompassing the totality of available clinical, economic, and humanistic evidence. Objective analysis of available randomized studies and real-world evidence is required, including long-term longitudinal studies evaluating economic and humanistic outcomes (i.e., health care resource utilization, work productivity, patient reported outcomes and patient preference). In contrast, value assessments, such as those put forth by ICER, utilize an incomplete approach to evidence and opinion-based assessments, and as a direct result, provide an incomplete answer to whether a given treatment offers value.[1] As one example of how ICER does not perform full value assessments for the therapies selected for evaluation within its UPI report, ICER excludes indications that represent less than 10% of a product's utilization. In doing so, ICER is potentially minimizing the impact of a product on rare conditions with small populations where therapeutic options are often limited such as hidradenitis suppurativa (known as "HS"), a rare orphan disease for which HUMIRA is indicated to treat.

Revealingly, ICER itself admits that its approach is limited and not comprehensive, via a disclosure written within its UPI Protocol: *"…ICER does not currently have the capacity to perform full economic analyses on the large number of therapies that will be subject to analysis as part of this report process, nor would the time needed to develop full ICER reports (at least*

eight months) provide information in a useful timeframe for the public and policymakers."[2] In their Report on US Value Assessment Framework, the ISPOR Special Task Force warns of this risk, *"…attempting to simplify the problem of value assessment, [value] frameworks could end up making ad hoc assumptions and simplifications not supported by theory or evidence, and thus may not deliver promised value."*[3] Despite ICER's own recognition that it lacks the capacity to perform the full economic analyses that would be necessary to arrive at the conclusions in this report and the feedback from multiple stakeholders over the last several years regarding the flawed methodology, the UPI report is published every year without addressing these limitations. Further, ICER disregards the fact that there are no recognized scientific or even ICER-defined standards to determine how much of a price increase is supported based on new clinical evidence. The result of this opaque process is an UPI report that seems to be based on the judgement of ICER reviewers determining whether they feel a price increase is supported based on their opinion of the new evidence available.

ABBVIE SUBMITTED EVIDENCE SHOULD BE CONSIDERED

Since its FDA approval in 2002, HUMIRA has helped transform care for 1,000,000+ patients who suffer from the effects of immune-mediated diseases. AbbVie's dedicated investment in HUMIRA research and development has resulted in multiple indications to serve patients living with a variety of immunological diseases including HS and has also resulted in patient-centric innovations (e.g., citrate-free HUMIRA, new dosing configurations). AbbVie has also been committed to developing and maintaining patient support programs that have been proven to help advance and improve the patient experience (e.g., AbbVie Complete, AbbVie's Patient Assistance Programs).

The cumulative impact of AbbVie's decades-long investment and innovations is that HUMIRA is today a therapeutic option available to a diverse set of patients suffering from ten different immune-mediated diseases in the U.S., including pediatric diseases, and orphan or rare diseases for which patients have limited treatment options. This outcome cannot be underemphasized: at its launch in December 2006, HUMIRA was only approved to treat a single disease. Twenty years later, AbbVie's ongoing research remains committed to HUMIRA and its proven ability to help patients achieve their treatment goals.

AbbVie provided evidentiary support that included recently published data evaluating the real-world use of HUMIRA and the positive impact on patients. ICER rejected each of these studies and stated they were either "published outside the timeframe of review" or "intervention/comparison not relevant to scope." AbbVie believes real-world data related to the patient experience with a product is highly relevant and needed to assess the value of therapy. As such, we disagree with ICER's assertion that such data is not relevant to their assessment.

Beyond ignoring HS, ICER ignored all other HUMIRA indications that represent less than 10 percent of HUMIRA's use. In limiting the assessment to indications representing greater than 10 percent use, ICER excluded HUMIRA's clinical and economic value in smaller patient populations, including rare conditions (i.e., HS and uveitis {non-infectious intermediate, posterior, and pan uveitis: NIIPP} juvenile idiopathic arthritis and pediatric Crohn's disease) and orphan indications (i.e., pediatric ulcerative colitis, pediatric uveitis (NIIPP), and adolescent hidradenitis suppurativa that reflect our commitment to innovation and improvement in net

health benefit.[4] By consistently excluding evaluation of a product's value in small patient populations with limited treatment options, ICER minimizes patients' needs and dismisses the significant benefit and value a medicine brings .

Finally, it is important to note that while drug list price (Wholesale Acquisition Cost, WAC) is well established, list prices are not what health plans and federal programs like Medicare and Medicaid ultimately pay for drugs. ICER recognizes this by including a calculation of net price impact in their analysis. The net price increase calculated by ICER (1.95%) is well below the Medical CPI, a benchmark used by ICER to determine inclusion in the report – though it is only applied by ICER to WAC price changes. If ICER compared net price increase against Medical CPI, a measure that would be more closely associated with what is paid by plan sponsors, HUMIRA would not be included in this report. Further, ICER identifies a net spending increase of $386 million. This notation by ICER is added for dramatic effect given that ICER does not identify that the net spending increase is based on the number of patients using and benefiting from HUMIRA. Products with a smaller number of utilizers have less net spend. In this respect, HUMIRA is penalized for having a breadth of indications as well as broad patient impact.

As outlined above, AbbVie believes that the totality of evidence must be evaluated as part of any value measurement. Further, AbbVie believes ICER continues to dismiss concerns that there are no recognized scientific or even ICER-defined standards to determine how much of a price increase is supported based on new clinical evidence. The result of this opaque process is an UPI report based on the opinions of ICER reviewers. We vehemently disapprove of this methodology, which is not informed by the totality of evidence that exists for a product.

AbbVie is committed to discovering and developing transformative therapies that advance the standard of care and improve patient experiences in a number of therapeutic areas. Continuous innovations like these require significant ongoing investment; such investment and innovation has continued to return value to patients, healthcare providers and policymakers and yet is not reflected in ICER's methodology or report.

AbbVie hopes that stakeholders can come together to understand value holistically and to continue pursuit of and support for sustainable, system-wide solutions while protecting scientific innovation and access to breakthrough treatments. We believe ICER's flawed methodology of its UPI Assessment must be addressed to help ensure complete and reliable conclusions around value, and to ensure payers, policymakers, and patients can properly weigh value and access for the vital innovative therapies that they need and deserve.

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Amgen Response to ICER's 2023 National UPI: Manufacturer Input II

Amgen appreciates the opportunity to comment on ICER's *2023 National Unsupported Price Increase (UPI) of 1) Prolia®, 2) XGEVA®, and 3) Nplate®*. Amgen is dedicated to ensuring the responsible pricing of its products, recognizing the crucial role cost plays in enhancing access to essential treatments for patients. We stand behind the value of Prolia, XGEVA, and Nplate in managing debilitating diseases and improving patients' quality of life. These products are supported with robust clinical and real-world evidence, including several ongoing studies where data will continue to become available over the coming months.

Amgen regrets that ICER has disregarded compelling new evidence within ICER's review period in over 700,000 patients supporting the value of Prolia.[1,2,3,4,5] These new data differentiate Prolia as an effective and cost-saving treatment for osteoporosis by reducing the risk of fractures, strengthening bones, and improving bone density compared to generic oral bisphosphonates and alendronate.[6,7,8,9,10] Additionally, in a study of long-term outcomes, the open label extension study of the FREEDOM clinical trial showed that up to 10 years of Prolia use continuously improved bone microarchitecture.[11] Real-world claims analyses also found that Prolia users were more persistent at one, two, and three years compared to oral bisphosphonate initiators.[12] This conclusion was further substantiated by additional real-world evidence analysis of fracture outcomes.[13] Another retrospective, claims-based study identified no increased risk of myocardial infarction or stroke compared to zoledronic acid for up to 36 months of treatment.[14] This new evidence supports long-term tolerability and safety, which are especially important for a chronic condition like osteoporosis. Prolia was also cost-effective – and in some cases, cost-saving – in a number of studies between 2021-2022.

Amgen also opposes ICER's interpretation of Nplate's data and new indication in Hematopoietic Acute Radiation Syndrome (H-ARS) as well as its new data in Immune Thrombocytopenia (ITP). In 2020-2021, robust new data in H-ARS led to an expansion in Nplate's FDA approval, and additional new evidence has bolstered its clinical benefits in ITP. The FDA's approval of Nplate to increase survival in H-ARS in adult and pediatric patients was supported by a number of pre-clinical studies under the animal rule demonstrating statistically significant improvements in survival and key hematologic parameters following potentially lethal radiation exposure.[15,16,17,18] Unfortunately, ICER has excluded H-ARS as comprising less than 10% of use, diminishing the value of Nplate's approval in this rare but deadly indication and its unique role in U.S. national security. Additionally, several publications on Nplate's use in ITP shed new light on its immunogenicity, tapering, and use in newly diagnosed patients as well as those with severe bleeding, yet ICER did not consider these.[19,20,21,22]

Recommendations

1. Change Prolia's rating to "supported" given new, meaningful, regulatory grade evidence on over 700,000 patients.

Considering recent CMS initiatives and the FDA's real-world evidence (RWE) framework designed to accelerate treatment access under the 21st Century Cures Act, ICER is out of step with current acceptance and thinking on RWE.[23,24] ICER should adopt a more comprehensive approach that embraces the use of RWE and moreover, non-RCT data to better align with the evolving landscape.[25,26,27] Amgen submitted two high-quality real-world studies supporting Prolia, which ICER categorized as "low quality." The first was a comparative effectiveness analysis of claims from 22,618 Medicare Advantage

and commercial patients, providing new evidence that Prolia reduced fracture risk compared to alendronate.[28] The second was a retrospective cohort study of 542,941 Medicare patients, indicating greater persistence in Prolia vs. oral bisphosphonate users.[29] Despite being within the timeframe and scope of ICER's review, these robust findings of real-world clinical benefits were deemed insufficient. The reasoning provided for the low rating of Kim *et al.*, 2022 was, *"the absence of specific criteria that would increase the quality of evidence."* However, researchers, regulatory bodies, and academics have embraced real-world evidence with very clear recommendations for incorporating and assessing it. There is wide recognition that properly designed RWE can mirror results from clinical trials while answering questions that randomized clinical trials cannot. In the interest of alignment with contemporary research and capturing the lived patient experience, we encourage ICER to recognize that RWE can and should be held to specific standards, which are met by our submitted studies.

Though Amgen recognizes the intention to align the evidence review period and the pricing timeframe, we encourage ICER to consider that pricing decisions reflect internally available data that may not be accessible in the public domain. For example, results from the Curtis *et al.* study have been available to Amgen since 2022, and it would be a fundamental oversight to ignore this compelling real-world evidence of Prolia's comparative effectiveness.[30] In a cohort of nearly half a million Medicare patients, this analysis demonstrated robust and significant reductions in the risk of hip, nonvertebral (NV), non-hip/nonvertebral (NHNV), and major osteoporotic (MOP) fractures for real-world patients on Prolia compared to alendronate. This study and the Kim *et al*. study are valuable additions to the literature, achieving head-to-head comparisons of fracture risk reduction not previously attempted in clinical trials.[31] Further, Curtis *et al*. is *regulatory grade* evidence that abides by FDA guidance, representing the highest possible caliber of real-world research: this may be the largest and most robust real-world study ever conducted in osteoporosis. Each of these studies provides strong evidence on their own, but combined, give exciting insights that go beyond clinical trials and head-to-head comparator information that has never been studied in trials. Accordingly, ICER's evaluation of the literature ignores a plethora of evidence addressing the knowledge gaps that clinical trials simply cannot fill.

2. Change Nplate's rating to "supported" given the investment in and successful FDA approval of a new indication.

ICER's decision to dismiss Nplate's new H-ARS indication as representing <10% of its potential usage is grounded in impractical uptake projections. ICER's protocol states that it will only consider supporting evidence in an indication currently below 10% of overall use "*if manufacturers report that use is rapidly increasing*." However, ICER has failed to account for the value Nplate provides in H-ARS – an uncommon but debilitating condition. The onset of H-ARS is limited to circumstantial radiation exposure, requiring the proactive development of novel therapeutics before catastrophic events occur. Contrary to most disease areas where treatments are developed in response to data demonstrating unmet need, Nplate's value in treating H-ARS cannot be adequately assessed without special consideration surrounding the unique manifestation of this condition. To move science forward and simultaneously protect the needs of rare disease patients under the Orphan Drug Act, it is important that indications are neither discounted nor prioritized according to the number of patients that suffer from that disease.

ICER fails to consider Nplate's unique applications and its role in U.S. national security. It should be noted that H-ARS is an incredibly specific indication associated with intense radiation exposure from atomic bombings, nuclear powerplants, and sterilization radiators.[32] An indication that cannot be ethically tested in humans is unlikely to, and hopefully will *never*, comprise more than 10% of use. It is important that innovation in these rare conditions not be undermined simply because of the timing of approval vs. use, particularly for products like Nplate that could one day be critical to national security and public health. As exhibited by the fallout of the COVID-19 pandemic, preparation for these unforeseen national emergencies can save countless lives and incalculable long-term costs.

The exclusion of Nplate's FDA-approved label based solely on it being categorized as a "*study protocol/editorial/conference citation with no abstract*" appears to be a very literal interpretation of ICER's criteria and raises questions regarding the validity of ICER's approach. Amgen provided Nplate's FDA prescribing information as the foundational evidence supporting the approval of a new indication within ICER's timeframe. As with all FDA labels, it captures every relevant clinical study and explicates how these data demonstrate net benefit and qualify the drug's suitability for real-world use. The downgrading of an FDA label – representing the ultimate benchmark of efficacy, safety, and regulatory acceptance – suggests ICER is putting its own criteria ahead of the FDA's.

Conclusion

Compelling new evidence in recent years has demonstrated Prolia and Nplate's clinical and real-world value. High-quality claims data have offered head-to-head evidence of Prolia's advantages over alendronate, while extensive studies in Nplate led to a new FDA-approval in H-ARS that enhances national security and preparation for "never events." ICER should keep pace with regulatory, disease, and scientific communities' broad and expanding embrace of real-world evidence and apply the established standards for assessing its quality, rather than discounting non-RCTs entirely. ICER must also reconsider the validity of its protocol restrictions and review its criteria to avoid disregarding the importance of label expansions into rare diseases or excluding universally endorsed sources like FDA prescribing information. Amgen stands behind the value of its products and maintains a commitment to serving patients through innovation, responsible pricing, and excellence in research.

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Bausch Health ("Bausch") is committed to continued research across our portfolio with the goal of providing robust clinical and health economic data for informed decision-making by our stakeholders. In tandem, our utmost priority is to maximize affordable access to therapies, which has driven our approach to XIFAXAN® (rifaximin 550 mg tablets), a critical medication for managing hepatic encephalopathy (HE) and irritable bowel syndrome with diarrhea (IBS-D).

We have actively collaborated with ICER during previous Unsupported Price Increase (UPI) cycles (2020-2022) and provided 28 (2020 UPI cycle) and 25 (2021 UPI cycle) peer-reviewed publications during the Manufacture response Phase I. We strongly believe that the evidence provided to ICER in previous UPI cycles systematically demonstrated the clinical and economic value of XIFAXAN in HE and IBS-D, but they were disregarded by ICER. We would like to reiterate our disappointment and disagreement with ICER's review process, which we believe is narrow and restrictive, and completely disregards the most recent critical peer-reviewed evidence leading to an incomplete picture of Xifaxan's value for US patients and payors. Specifically, we would like to highlight that ICER independently identifies new information from randomized clinical trials (RCTs) only and does not look for information other than RCTs (section *4.1.2* of the ICER UPI protocol):

1. *"ICER will then perform* ***independent systematic reviews looking for new information from randomized controlled trials (RCTs)*** *on benefits and harms within these indications published or presented during our Evidence Review Periosd."*
2. "***ICER will not independently look for information other than from RCTs*** *but will assess RCT and non-RCT information published or presented during our Evidence Review Periods that is submitted by manufacturers*."

Though ICER assesses information other than RCTs that are submitted by the manufacturers, as previously mentioned, ICER has been dismissive of the quality of evidence submitted by Bausch during previous UPI engagements. For example, during the 2022 Manufacturer Input response Phase II (final report poster December 6, 2022), we categorically highlighted ICER's inappropriate characterization of the Jesudian AB, 2020[1] (cost-effectiveness evidence supporting XIFAXAN for HE) study during the 2020 ("Study published outside of the timeframe of our review") and 2021 ("Previously known information about rifaximin related to cost") UPI cycles.

Bausch would like to acknowledge that for the 2023 Manufacturer Input Response Phase II, ICER's search identified 19 articles of which 0 were screened as full text. The full text articles associated with these 19 articles may contain valuable information in the manuscript body but not reported in the abstract. We would like to note that the Abdel Moneim M, 2021,[2] study screened by ICER is an open-label parallel, prospective interventional study, assessing outcomes of 400 mg rifaximin 3 times daily plus lactulose 3 times daily compared to lactulose alone amongst HE patients with Hepatitis C virus-related cirrhosis. This study showed that the resistance to rifaximin (measured as difference in minimum inhibitory concentration of rifaximin of intervention vs control) was not significantly different amongst those in the rifaximin group

(vs lactulose alone). However, the authors reported that those in the rifaximin group had significantly lower risk of developing HE and the time to first episode of HE event was longer. Further, the authors also found that none of the rifaximin-associated adverse effects were life-threatening or required hospitalization over the 6-month study period. Another study that ICER screened is the study by Zeng X, 2021,[3] a multi-center open label prospective study, which assessed the outcomes of low dose rifaximin 400 mg twice daily for 6 months compared to conventional therapy in patients with decompensated liver cirrhosis. This study showed that low dose rifaximin reduced overall complications, had no significantly different effect on transplantation-free survival, but markedly reduced the episodes of ascites exacerbation, HE and gastric variceal bleeding. While the dose used in these studies (i.e. 400 mg rifaximin 3 times daily [Abdel Moneim M]; 400 mg twice daily [Zeng X]) and the on label study population does not conform to the FDA-approved XIFAXAN label for HE, the studies do show rifaximin's value in terms of lowering the risk of development of an HE episode and time to HE episode in line with the FDA label.

We would like to highlight a few important studies published within the 2023 ICER UPI review period (i.e., January 2021 – December 2022) that highlights evidence supporting the value of XIFAXAN. The Volk ML, 2021,[4] study is a real-world evidence study that highlights the reduction in healthcare utilization (HE-related and all cause IP admissions and days) and costs associated with the use of and adherence to rifaximin (vs lactulose alone) amongst commercially insured patients with HE using Marketscan Commercial claims and Optum Clinformatics Data Mart databases. When considering the study results in a simulated plan of 1 million lives, if payors and physician ensured adherence to rifaximin, the total cost savings would be $5.9 million per year ($0.49 per-member-per-month [PMPM]) using results from Marketscan and $4.4 million per year ($0.37 PMPM) using results from Optum. Additionally, if 50% of patients with HE who were treated with lactulose alone had rifaximin added on and were adherent to their rifaximin therapy, the total cost savings would be-- $7.5 million per year or about $0.62 PMPM (Marketscan); $6.1 million per year or $0.50 PMPM (Optum). The Volk ML, 2021 study findings have been central to payor interactions and have enabled several payers to make key decisions on XIFAXAN coverage.

A single-center retrospective cohort analysis by Chang C, 2021,[5] compared the long-term efficacy (1-year) of rifaximin add-on to lactulose versus lactulose alone among adults with at least 2 episodes of HE. Outcomes assessed were time to first HE recurrence (Conn score ≥ 2), numbers and days of hospitalization attributed to HE and certain laboratory/clinical parameters (e.g., serum ammonia level, Mini-mental state examination, etc.) Patients treated with rifaximin + lactulose vs lactulose alone had a significantly longer median time (204.50 days vs. 125.00 days; $p = 0.044$) to first HE recurrence (Conn score ≥ 2) and significantly lower odds (odds ratio: 0.214 [$p = 0.045$]) of experiencing HE recurrence. Treatment with rifaximin + lactulose (vs lactulose alone) led to a lower number of HE hospitalizations (median 1 vs. 3; $p < 0.001$] and days of HE hospitalization [median 11 vs. 37; $p = 0.003$].

Hudson M, 2021,[6] in a retrospective observational extension study assessed the long-term survival (5-year) in HE patients receiving rifaximin-α treatment. The median (interquartile range) survival was 2.8 (0.8−5.0) years with 1-, 3-, and 5-years survival rate following rifaximin-α treatment of 72%, 49% and 35%, respectively. Approximately one third of patients (35%) on rifaximin-α survived after 5 years which compared favorably with 15% survival at 5 years reported in similar patients not receiving rifaximin-α (Jepsen P, 2010[7]).

We would further like to highlight key real-world evidence studies published in 2023 supporting the value of XIFAXAN, that have been critical for payor interactions.[8-11] Jesudian AB, 2023,[8] assessed the impact of rifaximin (± lactulose) use following discharge of an initial overt hepatic encephalopathy (OHE) hospitalization on OHE rehospitalizations and healthcare costs among commercially insured OHE patients. The study results highlight that those treated with rifaximin (vs. no rifaximin treatment) following discharge from initial OHE hospitalization had a significantly lower 30-day risk of experiencing OHE rehospitalization (44% lower) and a significantly lower annual rate of OHE hospitalizations (59% lower). Further, when the study cohorts were stratified into four subgroups representing decreasing quality of care (QoC; Type 1: Received rifaximin without any time gap following the index OHE hospitalization; Type 2: Received rifaximin within 30 days post-discharge; Type 3: Received lactulose within 30 days post-discharge; Type 4: Received no rifaximin/lactulose within 30 days post-discharge), results showed that decreasing QoC (type 1 to type 4) was associated with a higher risk of 30-day rehospitalization and higher annual rates of hospitalization. Finally, reduced medical costs in the rifaximin treatment cohort offset the increased pharmacy costs, resulting in no significant total cost differences observed between the rifaximin treated vs not treated cohort. Findings from this study highlight the importance of treating patients with rifaximin immediately following an OHE hospitalization to reduce the risk of future OHE hospitalizations and economic burden.

A study by Wong R, 2023,[9] assessed the trends of cirrhosis prevalence, OHE prevalence, OHE hospitalizations and costs, and XIFAXAN use and costs from 2006-2020 among a commercially insured population. Findings from this study show that the prevalence of cirrhosis and OHE increased by 5.2% year over year (YOY) and 4.4% YOY, respectively. Further, the rates of OHE hospitalization using various definitions decreased from 32.3%-56.0% to 5.5%-28.4% (2006 to 2020). Utilization of XIFAXAN increased from 2.2% in 2010 (XIFAXAN for HE approved in 2010) to 6.3% in 2020. Of note, the cost of OHE hospitalization increased by 4.5% YOY from 2010-2020 ($39,333 to $77,699) and especially a marked increase ($38,193 to $77,699) from 2015-2020 (8.1% YOY). During the 2015-2020 period, though monthly XIFAXAN cost increased from $1,811 to $2,389, the YOY increase of 4.5% was lower than the YOY increase of costs of OHE hospitalizations during the same period. The findings of this study highlight that the prevalence of cirrhosis and OHE over time increased; rates of OHE hospitalizations decreased but the cost of OHE hospitalization increased; the YOY increase in cost of XIFAXAN was lower than the YOY cost increase of OHE hospitalization.

Jesudian AB, 2023,[10] assessed the impact of gaps in XIFAXAN access due to prescription claim rejections on OHE hospitalizations and costs. This study highlights that rejection-related gaps in

access to XIFAXAN were associated with a significantly higher risk (incidence rate ratio of 1.55-3.19) of experiencing OHE hospitalization compared to no rejection related gaps of XIFAXAN, with the risk of OHE hospitalization increasing with the length of access gap (≥7 to ≥ 21 days). Further, longer length of rejection-related access gaps was associated with higher total medical costs ($1,579-$3,413 PMPM) compared to no rejection related gaps. Findings from this study highlight the importance of having continuous access to XIFAXAN to reduce the risk of OHE hospitalization and increased healthcare costs.

Of importance, there was no OHE-specific *International Classification of Diseases, Tenth Revision (ICD-10)* code from October 1, 2015, to September 30, 2022, which may have led to an underestimation of the burden of OHE. Jesudian AB, 2023,[11] using in-hospital database (October 1, 2015-June 30, 2022) developed an algorithm to identify an active OHE hospitalization event. Hospitalizations with ≥1 dose of in-hospital rifaximin or lactulose, and ≥1 ICD-10 code for altered mental status, unspecified encephalopathy, and/or cirrhosis or its complications (i.e., varices, hepatorenal syndrome, spontaneous bacterial peritonitis) were identified as an active OHE hospitalization event. Hospitalizations identified using this criterion for OHE hospitalization on average had 2.0X longer length of stay and 2.5X times higher hospitalization billing charges compared to hospitalizations identified based solely on a primary diagnosis of OHE (OHE hospitalization defined using Centers for Medicare & Medicaid Services General Equivalence Mappings). Findings from this study highlight that the burden of OHE (rate, length of stay, and associated costs) has been likely underestimated, which may further highlight the importance of XIFAXAN for reducing the healthcare burden associated with OHE.

We strongly believe that the recent published evidence further underscores and enhances the value of XIFAXAN for HE. However, dismissing key pieces of recent and relevant evidence due to a restrictive evidence review period and search strategy trivializes this valuable evidence. This pattern of overlooking recent evidence potentially diminishes the submitted evidence and its value for making informed decisions by key stakeholders. In conclusion, we continue to disagree with ICER's UPI assessment protocol and how it continues to dismiss the multiple recent and relevant studies which provides US payors and patients relevant insights into the true value of XIFAXANs yet are likely to be categorized as "outside of the time frame".

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Genentech
A Member of the Roche Group

October 24, 2023

Institute for Clinical and Economic Review (ICER)
14 Beacon Street, Suite 800
Boston, MA 02108

Dear ICER Review Panel:

This letter is in response to ICER's draft 2023 Unsupported Price Increase (UPI) Report. Genentech appreciates the opportunity to comment on ICER's methods and its interpretation of the clinical evidence for Perjeta (pertuzumab).

To date, 260,000 patients have been treated with Perjeta in the US. Perjeta was initially approved for HER2-positive (HER2+) metastatic breast cancer (mBC) in 2012 for use in combination with Herceptin (trastuzumab) and docetaxel in patients who have not received prior anti-HER2 therapy or chemotherapy. In 2013 it was granted accelerated approval for neoadjuvant treatment of patients with HER2+, locally advanced, inflammatory or early stage breast cancer (eBC). Most recently, in 2017, it became the first FDA-approved treatment for adjuvant use in patients with HER2+ eBC at risk of recurrence and the accelerated approval in the neoadjuvant setting was converted to full approval. Since its initial approval in 2012, Perjeta has provided significant innovation in the treatment of breast cancer through improved progression free, disease free, and overall survival and related impacts on health-related quality of life. Genentech has remained committed to investigating the performance of Perjeta across new indications and subpopulations, and to generating evidence on the value Perjeta brings to patients and their families, health systems, and society.

In reviewing the draft UPI report, we are concerned with ICER's flawed methodology regarding the UPI assessment for Perjeta®, including ICER's conclusion that Perjeta's price increase was unsupported by clinical evidence. Specifically, we recommend that ICER:

1. **Change the conclusion for Perjeta to be *supported by new clinical evidence* given the recognized impact of this practice changing data in the medical community.**

2. **In alignment with ICER's own approach to value assessment, consider evidence beyond randomized clinical trial data that demonstrates the impacts of Perjeta on patients and their families, the healthcare system and society overall.**

3. **Revise methods or discontinue the UPI report given that its flawed methodology presents an unbalanced and narrow picture of both drug value and investment in clinical research.**

We expand on our recommendations below:

<u>Recommendation 1:</u> Change the conclusion for Perjeta to be *supported by new clinical evidence* given the recognized impact of this practice changing data in the medical community. As outlined in the data submitted to ICER, five clinical studies were published between January 2021 and December 2022 highlighting Perjeta's efficacy in diverse contexts. These findings collectively expanded our

understanding of pertuzumab's therapeutic potential across various clinical scenarios (see Table 1 below) and resulted in practice changing recommendations by the National Comprehensive Cancer Network® (NCCN®). Earlier this year, the NCCN revised their eBC guidelines, elevating pertuzumab/trastuzumab to a Category 1 preferred recommendation for HER2-positive, node-positive patients, irrespective of hormone receptor (HR) status [1]. Moreover, the NCCN also recommended the inclusion of pertuzumab and trastuzumab as a treatment option for brain metastases in patients with HER-2 positive breast cancer (category 2A) in 2022 [1]. Both recommendations were based on the latest APHINITY and PATRICIA trials, which we submitted to ICER but they declined to include in their assessment.

Table 1: Summary of New Clinical Evidence Submitted to ICER

New Evidence	Impacts/Implications
Loibl et al 2022 [2]: New evidence confirms long-term efficacy of pertuzumab in eBC patients with a high risk of recurrence.	The APHINITY trial has had a significant impact on clinical practice. With 8.4 years of median follow-up, it has presented compelling evidence that pertuzumab's benefit in HER2+ eBC endures, with the greatest advantages seen in the N+ cohort, irrespective of HR status. Results from the updated trial prompted NCCN to elevate the combination of pertuzumab and trastuzumab to Category 1 status for this population, playing a pivotal role in shaping treatment strategies for high-risk eBC patients [1].
Swain et al 2022 [3]: New evidence reinforces the clinical benefits of pertuzumab in eBC neoadjuvant to adjuvant treatment continuation.	Evidence from the pooled analysis suggests that pertuzumab, in combination with trastuzumab, provides the most clinical benefit, when included in both neoadjuvant and adjuvant setting among patients with HER2+ eBC who have a pathological complete response after neoadjuvant HER2-targeted therapy plus chemotherapy. The results reinforce the clinical benefits of pertuzumab in eBC.
Lin et al 2021 [4]: New evidence supports the efficacy of pertuzumab in central nervous system (CNS) metastases, a population with high unmet need.	Based on the evidence from the Phase II PATRICIA trial, and a non-pre-specified exploratory analysis of the pivotal Phase 3 CLEOPATRA, pertuzumab, in combination with trastuzumab, is now guideline recommended as a viable option for treating brain metastases in previously untreated HER2+ mBC [5].
Yamamoto et al 2022 [6]: New evidence supports the efficacy of pertuzumab retreatment in later treatment lines.	The PRECIOUS study revealed that retreatment involving pertuzumab, trastuzumab, and chemotherapy in advanced HER2+ breast cancer patients, who had received prior pertuzumab-containing regimens, led to a notable improvement in progression-free survival (PFS). These results provide evidence for the potential efficacious effect of dual HER2 blockade with pertuzumab as an additional treatment choice in later lines of therapy for these patients.

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New Evidence	Impacts/Implications
Takahashi et al 2021 [7]: New evidence supports the efficacy of pertuzumab in Japanese patients who previously did not show benefits in the CLEOPATRA trial.	The COMACHI study confirmed that the combination of pertuzumab plus trastuzumab and docetaxel is efficacious and well-tolerated in Japanese patients with HER2+ recurrent or mBC, hence providing patients with more efficacious treatment.

Recommendation 2: In alignment with ICER's own approach to value assessment, consider evidence beyond randomized clinical trial data that demonstrates the impacts of Perjeta on patients and their families, the healthcare system and society overall. ICER's decision to dismiss the clinical evidence we provided is disappointing. For example, ICER opted not to evaluate the extent of benefits in cases where evidence is available from phase II clinical trials. This decision was made despite the inherent challenges of conducting phase III clinical trials, as in the case of the PATRICIA study that evaluated the effect of Perjeta among patients with HER2+ mBC with CNS metastases [4]. It is worth noting that HER2Climb was also a Phase II trial yet the FDA approved label for CNS mets. And both PATRICIA and HER2Climb studies received NCCN CNS listings [5]. For years, patients with breast cancer and brain metastases were typically excluded from clinical trials due to the prevailing belief that anticancer drugs couldn't effectively penetrate the blood-brain barrier [8]. The PATRICIA study, however, emerged as one of the first studies to provide compelling evidence that systematic targeted therapies can indeed benefit patients facing these substantial unmet medical needs. The results of the PATRICIA study, along with other clinical evidence, led to the NCCN panel uniformly recommending the inclusion of pertuzumab and trastuzumab as a viable option for patients with HER2+ breast cancer and brain metastases, receiving a category 2A recommendation in 2022 [5]. This underscores a significant disconnect between ICER's perspective on what constitutes reliable evidence versus the medical community dedicated to the care of these patients. Similarly, ICER decided to dismiss clinical evidence supporting retreatment of patients with advanced stages of their cancer, another high unmet population.

The value of Perjeta extends beyond the scope of the studies that ICER are willing to review in their UPI report. While their assessments have been confined to specific clinical trials and data within a limited arbitrary timeframe, it's crucial to recognize that new and evolving evidence continues to emerge, offering a more comprehensive perspective on Perjeta's impact. A prime example of this is a recent model that translates individual outcomes into projected population benefits of Perjeta in preventing recurrence among a substantial cohort of HER2+ eBC patients. According to this model, the use of Perjeta in both neoadjuvant and adjuvant settings is projected to prevent 20,596 recurrences between 2013 and 2031, resulting in over $8.5 billion in healthcare cost savings during the same period [9,10]. This projection underscores the substantial and long-lasting positive effects that Perjeta can have on both the patients and the US healthcare system.

Recommendation 3: Finally, we recommend that ICER either revise methods or discontinue the UPI report given that its flawed methodology presents an unbalanced and narrow picture of both drug value and investment in clinical research. Year over year, ICER receives consistent criticism about how the UPI report draws connections between pricing trends and evidence [11-13]. In particular, ICER makes conclusions on whether prices are *supported/unsupported* based on clinical trial data

published in an arbitrary two-year period preceding price changes. New evidence on the impact of treatments grows and proliferates over time based on new research questions learned through real world use of a medicine. ICER's decision to consider only the preceding two years of new evidence has no basis and it fails to appropriately value the significant ongoing investment in research for new indications, new delivery mechanisms, and other manufacturer-funded health system interventions that aim to improve patient outcomes and experiences. Further, ICER's current methods place almost a sole emphasis on randomized clinical data via use of the GRADE criteria and its narrow consideration of other forms of evidence. This approach fails to recognize that non-randomized trials may be the only suitable, ethical option to explore some outcomes and that real world data plays a vitally important role in exploring a broader range of clinical, economic and humanistic outcomes under routine care [14]. Many of the important ways treatments impact patients and their families and the healthcare system cannot be studied adequately in clinical trials alone.

ICER has stated that its goal as an organization is to *"provide the public and policymakers with information they can use to advance the public debate on drug price increases"* [11]. The methods used to assess whether a price increase is *supported* in the UPI report stand in stark contrast with ICER's approach to its core work on value assessment. As outlined in its newly updated value assessment framework, ICER clearly supports that decisions on treatments should include broader impacts beyond what is studied in clinical trials [15]. Information on price should be shared alongside balanced information on treatment's disease-related impacts across patients and other stakeholders, including information on quality of life, adherence, family spillover effects, unmet need, and others. The annual UPI report has failed to evolve alongside ICER's other activities. As it stands, the UPI report presents an unbalanced and narrow picture of investment in clinical research that cannot support informed debate on drug prices. It is time for ICER to reconsider whether the UPI report truly supports its goals.

We provide these recommendations with the hope that ICER will recognize Genentech's continued commitment to generating clinical evidence on Perjeta across new populations and lines of care to help ensure that the right treatments are delivered to the right patients at the right time in breast cancer care. Perjeta is a proven and efficacious treatment for HER2+ mBC and offers significant risk reduction of recurrence risk in HER2+ eBC patients. As outlined above, we believe ICER's current approach to assessing the value of new evidence is unbalanced and conflicts with its own approach to drug assessments and its stated goals as an organization. To ensure that the 2023 National UPI report presents a fair and balanced view of the value of Perjeta, we recommend that ICER update their conclusions to recognize the impactful new clinical data outlined herein, which demonstrates impact in new populations with high unmet need. As always, we offer our assistance in further discussing the evidence provided to support ICER's UPI assessment of Perjeta.

Sincerely,

Jan Elias Hansen

Jan Elias Hansen, Ph.D.
Vice President, Evidence for Access
Genentech, U.S. Medical Affairs

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October 20, 2023

Steven D. Pearson, MD, MSc, FRCP
President
Institute for Clinical and Economic Review (ICER)
14 Beacon Street
Boston, MA 02108

Re: UPI Preliminary Assessment of Jakafi®, Price Increase Supported by Evidence

Dear Dr. Pearson,

Incyte appreciates the opportunity to comment on ICER's preliminary Unsupported Price Increase (UPI) Assessment of Jakafi® (ruxolitinib), in which ICER concluded that new clinical evidence supported the pricing of Jakafi in 2021-2022. Incyte firmly believes the pricing of Jakafi is well-supported by our expansive research and development program and the value Jakafi brings to patients, which ICER acknowledged in this assessment.

Jakafi Has Multiple FDA-Approved Indications to Treat Rare Diseases with Serious Unmet Need

Given Incyte's commitment to patients and ongoing investment in research and development, we agree with ICER's recognition that the value of Jakafi is clearly supported by new clinical evidence. Jakafi is an oral Janus-associated kinase 1 and 2 (JAK1/JAK2) inhibitor with a proven clinical and safety profile with over 10 years of experience. Jakafi is the only FDA-approved treatment across the orphan indications[1] of:

- Myelofibrosis (MF): intermediate or high-risk MF, including primary MF, post-polycythemia vera MF and post-essential thrombocythemia MF in adults (approved November 16, 2011);
- Polycythemia Vera (PV): in adults who have had an inadequate response to or are intolerant of hydroxyurea (approved December 4, 2014);

- Graft-Versus-Host Disease (GVHD):
  - steroid-refractory acute GVHD in adult and pediatric patients 12 years and older (approved May 24, 2019);
  - chronic GVHD after failure of one or two lines of systemic therapy in adult and pediatric patients 12 years and older (approved September 22, 2021).

Incyte Continues to Invest in Jakafi and Advance the Science Related to Its Uses

Since Jakafi was first approved, Incyte has continued to invest in developing evidence to better understand the real-world value Jakafi brings to patients and to discover the potential of Jakafi for additional patient populations with high unmet need.

Incyte agrees with ICER's determination that MAJIC-PV and REACH3 are trials of good quality that demonstrate "substantial benefit for ruxolitinib," reinforcing ICER's conclusion that Jakafi's pricing was supported during the timeframe of ICER's review.[2,3,4] MAJIC-PV was the first study to demonstrate a correlation between attaining a complete response and event-free survival in patients with hydroxyurea-resistant or intolerant PV. Additionally, this study demonstrated the relationship between ruxolitinib therapy and improved thrombosis-free survival and event-free survival in a long-term prospective study. The REACH3 evidence led to a new FDA-approved indication in chronic GVHD and a Category 1 upgrade in the National Comprehensive Cancer Network (NCCN) guidelines, which represents the highest level of evidence available supported by uniform consensus of experts that the treatment intervention is appropriate.

Incyte respectfully disagrees, however, with ICER's determination that real-world evidence (RWE) studies constitute "low-quality evidence." Our RWE studies have been recognized by the scientific community at global scientific congresses and in peer-reviewed hematology journals.[5,6,7] Importantly, the studies demonstrate the real-world impact of treatment with Jakafi on overall survival in MF in the post-approval setting and the economic value of Jakafi in real-world clinical use.

Incyte's Investments in R&D Demonstrates Our Commitment to Scientific Advancement

Incyte is driven by rigorous science and our pricing decisions allow us to invest in scientific advancements in areas of high unmet medical need. In 2021 and 2022, Incyte invested nearly $1.5B and $1.6B in research and development, representing 49% and 47% of the company's total net revenues, respectively. These research and development costs include investment as part of our

ongoing LIMBER (Leadership In MPNs Beyond Ruxolitinib) clinical development initiative. LIMBER is designed to improve and expand therapeutic options for patients with myeloproliferative neoplasms and includes the evaluation of combinations of Jakafi with other therapeutic modalities.

Incyte Responsibly Prices Our Medicines

Incyte responsibly prices our medicines and makes price revisions with consideration to the clinical value that our medicines deliver to patients, as well as patient access and overall market conditions. Incyte's submissions to ICER included examples of the clear clinical and related scientific evidence supporting the value of Jakafi.

Incyte is confident in the value of Jakafi to patients, and we are pleased that ICER's assessment of our clinical evidence acknowledges that value.

Regards,

Amy Hall
AVP & Head of Market Access, Distribution and Patient Access Services - Oncology
Incyte Corporation

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October 24, 2023
RE: ICER's unsupported price increase assessment for IBRANCE® (palbociclib)

Pfizer appreciates ICER's mission of ensuring that medicines remain affordable to patients who need them and appreciates the opportunity to comment on ICER's draft Unsupported Price Increase (UPI) preliminary assessment of IBRANCE. Pfizer respectfully disagrees with ICER's overall conclusion, ICER's decision to exclude publications based on their notion of new information being termed previously known, and ICER's designation of one provided study as providing low-quality evidence.

We are particularly concerned with the dismissal of several submitted publications as not providing new information. We believe that the studies do, in fact, provide results that were not previously known on key outcomes such as overall survival (OS), especially in the real world, which includes populations underrepresented in clinical trials. We would like to obtain a better understanding from ICER beyond the General Evidence Response (GER) on the criteria defining new information in general as more clarity is crucial for transparency into ICER's process and decision making. Also, given the corrected net price increase value as described below, we request ICER remove IBRANCE from the UPI list as we believe it is questionable whether IBRANCE remains in the top 15 drugs in terms of increased impact on spending, or alternatively designate IBRANCE as having had a "price increase supported by new evidence" from 2021 to 2022.

The net price increase of 4.45% taken for IBRANCE during the reference period is a fair reflection of the value IBRANCE brings.

Pfizer appreciates ICER's acceptance of the corrected 4.45% net price increase calculation. Pfizer is committed to ensuring that the price of medicines is a fair reflection of the value they bring and has adjusted the net price in reaction to inflationary pressure. As a comparison, US prices for medical care rose 4% from December 2021 to December 2022.[1] As such, we question whether IBRANCE remains in the top 15 drugs whose net prices have had the largest impact on US spending in that timeframe after having provided the net price percentage correction.

Pfizer's purpose is to create breakthroughs that change patients' lives, with affordability being a critical factor. Pfizer remains dedicated to improving access and affordability for patients who rely on our medications and work with an array of healthcare stakeholders to develop sustainable

solutions addressing these issues, including a potential reform to the current US healthcare system.

Pfizer has taken a proactive approach to address this challenge in multiple ways. For example, Pfizer provides discounts, rebates, and other fees to insurers, pharmacy benefit managers, federal government programs, and other key stakeholders in the healthcare ecosystem to ensure that our medicines are accessible and affordable to the patients who need them. Pfizer also provides patient support through multiple sources, such as a patient assistance program and numerous partnerships with cancer-related patient advocacy groups.

RWE complements findings from RCTs and yields pertinent new information for clinical decision making.

Pfizer appreciates that contrary to previous years, ICER seems to place a greater weight on RWE studies. We appreciate this as Pfizer has made considerable efforts to ensure that RWE studies are well designed, appropriately powered, and use reliable, valid, and fit-for-purpose data. However, we question the assertion that the submitted RWE studies do not provide relevant new information (two examples are provided below). This classification was presented without any explanation on why and thus lacks transparency.

Pfizer believes that though RCTs are the gold standard in determining the safety and efficacy of a drug in a controlled setting, RWE informs clinical decision-making, and when combined with RCTs depict a more complete picture of a therapy.[2] While treatment randomization decreases risk of bias and confounding in an RCT, patient populations are selected using strict eligibility criteria and are required to strictly adhere to treatment protocols that often do not reflect the typical patient mix and treatment procedures seen in clinical practice.[3] RWE may therefore provide both new and complementary treatment effectiveness and safety results for the overall patient population, including patients often underrepresented or absent in RCTs. For instance, OS represents a key outcome in cancer trials. However, in metastatic breast cancer, where patient survival is much longer than other tumor types, progression-free survival (PFS) is the typical primary endpoint, with OS as secondary due to OS results not being available for many years and the potential impact of multiple treatments post progression. This lag in OS results can sometimes be addressed by RWE, where real-world data are potentially available before large phase III clinical trials results. This was the case with IBRANCE, where rapid uptake post approval led to an availability of real-world OS data before final readout from the phase III RCT, PALOMA-2. Therefore, well-designed RWE has the potential to provide important new evidence that can complement RCTs.

Pfizer considers that all the provided RWE studies contain “new information on the efficacy or safety” of IBRANCE as they are focused on populations reflecting real-world US clinical

practice and including subgroups often underrepresented in clinical trials, e.g., elderly patients, African American patients, and patients with select metastases.

Pfizer would like to highlight two of the well-designed RWE studies that provided new information on the effectiveness of IBRANCE at the time of publication. Both studies compared the efficacy of palbociclib plus aromatase inhibitor (AI) compared with AI monotherapy using validated survival endpoints from the Flatiron Electronic Health Records dataset, a national database accounting for over 800 sites of care across the US.[4]

The first study we would like to highlight is DeMichele et al, 2021.[5] DeMichele et al, 2021, found that after adjusting for imbalances in baseline demographics and clinical characteristics using propensity score-based methods, US patients receiving palbociclib with letrozole (N=772) compared with letrozole alone (N= 658) in the first-line setting had a statistically significant 42% reduction in risk of disease progression and 34% reduction in risk of death. [5]

At the time of this publication, the only OS data available from RCTs on IBRANCE for patients receiving treatment in the first line was from the PALOMA-1 study, which was a small phase II study (68 patients receiving palbociclib and letrozole, and 81 patients receiving placebo and letrozole).[6] Additionally, the primary endpoint was PFS. Lastly, OS was a secondary endpoint, and the study was not powered to show a difference in OS.

Clearly the RWE study by DeMichele et al, based on a large sample size, provided new, relevant, and important information regarding IBRANCE's comparative effectiveness with respect to OS in the US.

The second study we would like to highlight is Rugo et al, 2022.[7 8] Rugo et al, 2022, found that after a similar adjustment method, 1,342 patients receiving palbociclib with AI versus 1,564 patients receiving AI alone in the first line-setting had a statistically significant 24% reduction in the risk of death and 30% reduction in risk of progression.[7 8]

At the time this publication was presented at the European Society for Medical Oncology Breast Cancer conference in May 2022, the only OS data available on IBRANCE for this indication was from the PALOMA-1 study. The primary endpoint in Rugo et al, 2022 was OS and was powered accordingly, while the secondary endpoint was real-world PFS. Additionally, this study is more reflective of US clinical practice as the patient population was broadened to include patients receiving any AI.

In sum, while RWE evaluates associations and is unable to determine causality, these large studies not only provide new information for the reasons described above, but they also reduce the uncertainty of relying on outcomes from limited RCTs.

Increasing the certainty of RCT findings yields new information that is important for patient and clinician decision-making.

Pfizer is committed to understanding the value of IBRANCE with long-term use as the certainty of outcomes are reinforced. For instance, Pfizer provided long-term pooled safety analysis from RCTs of palbociclib with endocrine therapy versus placebo with endocrine therapy.[9] As the first CDK 4/6 inhibitor approved, there was no previously known information on long-term safety signals for this drug class until this study. Therefore, such analyses support patient-physician clinical decision-making.

Pfizer believes that the indirect comparison study on patient-reported outcomes is of high quality.

At Pfizer, we believe that every patient deserves to be seen, heard, and treated as an individual with respect and care. Patient-reported outcomes help Pfizer understand how it can improve its therapies to better serve our patients. As such, we submitted a matching adjusted indirect comparison (MAIC) assessing the relative impact of IBRANCE with fulvestrant and abemaciclib with fulvestrant on patient reported quality of life.[10]

ICER has deemed this a low-quality study, with which Pfizer respectfully disagrees. The methodology used for the study is the gold standard for indirect treatment comparisons because the design adjusts for differences in patient baseline characteristics.[11] The authors also provided strong justification for the selected effect modifiers. Additionally, the authors viewed the EORTC QLQ-C30 and EORTC QLQ-BR23 as two distinct constructs, thereby supporting their selected method to adjust for multiplicity. To address ICER's concerns on risk of bias without clear prior protocol, Pfizer creates protocols for all real-world and comparison studies. While protocols for indirect comparisons are not routinely disclosed as is required for RCTs and observational studies, Pfizer is happy to provide this protocol to ICER to review if requested.

Conclusion

We respectfully disagree with ICER's assessment of an unsupported price increase and believe the ICER assessment leaves out important supporting evidence. Importantly, given the corrected net price increase of 4.45%, we believe that IBRANCE net price increase is in line with the medical CPI and should not have been considered in this process. Moreover, it does not capture the value that IBRANCE brings to this patient population. Pfizer recommends that ICER re-evaluate both their designation and classification of RWE studies, as they offer new and valuable information to the breast cancer community. We welcome the increased importance ICER places on RWE but ask for an improved general guidance document on what constitutes new information according to ICER to improve transparency of the evaluation process.

Pfizer is confident in the value of IBRANCE to patients with HR-positive, HER2-negative metastatic breast cancer and continues to invest in high quality breast cancer clinical trials and RWE studies to provide continued evidence to health care providers and patients.

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