Unsupported Price Increase Report

Unsupported Price Increases Occurring in 2021

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About ICER

The Institute for Clinical and Economic Review (ICER) is an independent nonprofit 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/.

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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

A+CHP	Brentuximab vedotin plus cyclophosphamide, doxorubicin, and prednisone
ACR	American College of Rheumatology
ASAS	Assessment of Spondyloarthritis International Society
CHOP	Cyclophosphamide, doxorubicin, vincristine, and prednisone
CI	Confidence interval
CMS	Centers for Medicare and Medicaid Services
CPI	Consumer price index
E. coli	*Escherichia coli*
FDA	Food and Drug Administration
GEP-NET	Gastroenteropancreatic neuroendocrine tumor
GER	General Evidence Response
HSCT	Hematopoietic stem cell transplantation
IBS-D	Irritable bowel syndrome with diarrhea
ICER	Institute for Clinical and Economic Review
MACE	Major adverse cardiovascular event
mg	Milligram
n	Number
RCT	Randomized controlled trial
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 fourth 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 (2021) in the United States (US); this information came from SSR Health LLC, an independent investment research firm. We then excluded from this list 101 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 149 drugs, we estimated, where possible, the increase in spending in the US during 2020-2021 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.

For this 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 2019-2020 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. One of these three drugs was included in last year's UPI report on the basis of its net price increase, and so we used our previous evidence review for this drug as part of this report. Overall, our protocol therefore produced a final list of 12 drugs with new evidence assessments for this year's report and a 13th drug that had been previously assessed.

We performed assessments on these 12 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 and/or performed an 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 the 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, seven were judged to have price increases unsupported by new clinical evidence. The unsupported net price increases of these seven drugs produced a total of $805 million incremental added costs to US payers in 2021.

Of the three Medicare Part B drugs selected due to list price increases, all lacked supporting new evidence for their price increases. For these drugs, patients paying 20% coinsurance under Medicare Part B would have seen increases in individual out-of-pocket spending due just to the price increases ranging from $1,200 to $3,200 per year.

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 examine data on drug price increases next year 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)	2020 to 2021 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			
Xifaxan® (Rifaximin)	7.94%	12.14%	$174.7
Invega Sustenna®/Trinza® (Paliperidone)	4.83%	7.32%	$170.4
Prolia® (Denosumab)	5.79%	6.11%	$123.8
Entyvio® (Vedolizumab)	6.30%	4.50%	$118
Promacta® (Eltrombopag)	7.06%	11.46%	$94.9
Rexulti® (Brexpiprazole)	6.70%	7.61%	$67.9
Lupron® (Leuprolide)	6.20%	10.0%	$54.9
Drugs with Price Increases with New Clinical Evidence†			
Cosentyx® (Secukinumab)	7.05%	6.82%	$183.0
Tremfya® (Guselkumab)	4.81%	8.89%	$129.4
Jakafi® (Ruxolitinib)	7.01%	3.80%	$78.3
Part B Drugs with Price Increases Unsupported by New Clinical Evidence			
Drug (Generic)	**2019-2020 List Price Increase**	**Increase in Spending Due to Price Increase (Total Population, Per-Patient§ (in Thousands)**	
Somatuline® Depot (Lanreotide)	11.20%	$33,000, $1.21	
Adcetris® (Brentuximab Vedotin)	9.23%	$14,000, $1.64	
Krystexxa® (Pegloticase)‡	11.78%	$13,800, $3.21	

WAC: wholesale acquisition cost

*Year-over-year percentage changes were estimated by averaging over the four quarterly changes in price (i.e., Q1 2020 to Q1 2021; Q2 2020 to Q2 2021; Q3 2020 to Q3 2021 and; Q4 2020 to Q4 2021).

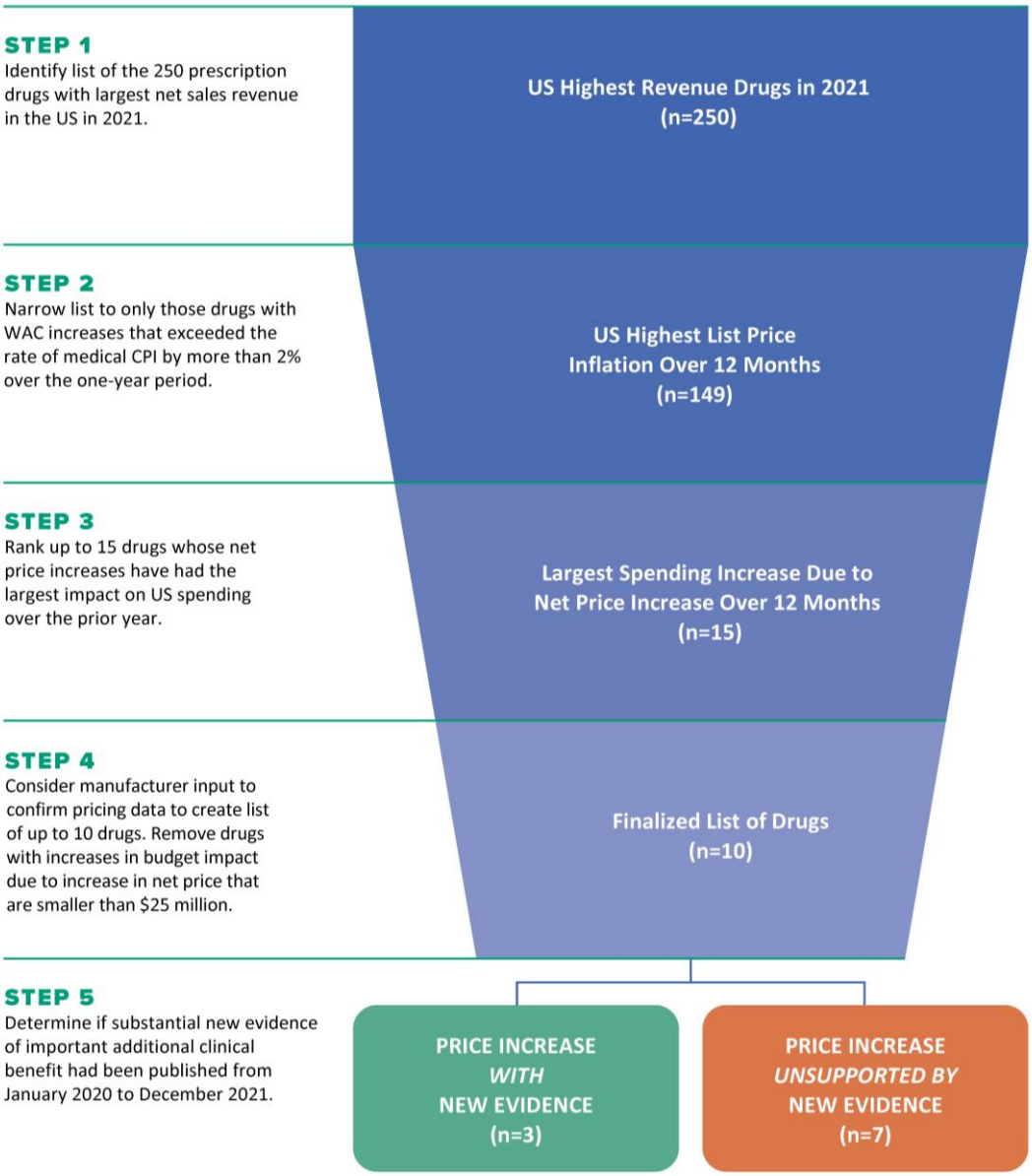
†This is not a determination that the new evidence necessarily justified these price increases.

‡Pegloticase had been previously assessed for the 2019-2020 time period in the prior UPI report and was found to have a net price increase unsupported by new clinical evidence. As such, under the protocol, pegloticase is identified as having had an important list price increase for this time period but is not re-reviewed for supporting evidence.

§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 12 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. Important changes for this year's report include changing the method for reviewing up to three additional drugs to focus on changes in list prices for Medicare Part B therapies and removal of drugs from the Main List if the increase in budget impact due to increase in net price was smaller than $25 million. The review of Medicare Part B therapies with increases in list price reflects concerns ICER heard about list price changes that potentially have large impacts on patients even if net prices do not change significantly. Under many insurance plans, including Medicare Part B, patients may be responsible for paying a percentage of the list price. The removal of drugs with small increases in budget impact was included because, in the prior UPI report, there were therapies included with changes in net prices that resulted in only small increases in spending.

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 over 1,000 drugs with net sales revenue in the US in 2021 from SSR Health LLC, an independent investment research firm. We then focused on those 250 drugs with the highest net sales revenue. For each of these 250 drugs, we then determined the average wholesale acquisition cost (WAC) price changes over a one-year period from 2020 to 2021. Please see Table 2.1 on the following page.

Table 2.1. List of Top 250 Drugs (Listed by Brand) with the Highest Net Sales Revenue (in Millions) in the US in 2021

Drug Name	Revenue†	Δ WAC‡
Ranking†: 1-50		
Humira§	**17,330**	**7.4%**
Keytruda	9,765	3.2%
Revlimid	**8,695**	**4.5%**
Comirnaty	7,809	-18.5%
Biktarvy	**7,049**	**4.8%**
Eliquis	**6,456**	**5.9%**
Stelara	**5,938**	**4.8%**
Regen-Cov	**5,828**	**342.8%**
Eylea	5,792	0.0%
Spikevax	5,348	i
Trulicity	**4,914**	**6.3%**
Dupixent	4,643	3.0%
Enbrel	**4,352**	**7.3%**
Imbruvica	**4,321**	**7.3%**
Opdivo	4,202	2.3%
Trikafta	4,170	0.0%
Ocrevus	**4,105**	**3.9%**
Veklury	3,640	-2.0%
Ozempic	**3,629**	**4.9%**
Ibrance	**3,418**	**5.1%**
Darzalex	**3,169**	**4.8%**
Entyvio	**3,097**	**6.4%**
Cosentyx	**2,883**	**7.1%**
Prevnar Family	**2,701**	**5.0%**
Invega Sustenna/ Trinza	**2,550**	**4.8%**
Xtandi	2,495	3.0%
Skyrizi	**2,486**	**7.4%**
Xarelto	**2,438**	**4.8%**
Orencia	**2,410**	**4.4%**
Vyvanse	**2,362**	**4.9%**
Soliris	2,343	-1.3%
Genvoya	**2,267**	**4.8%**
Pomalyst	**2,249**	**4.5%**
Prolia	**2,150**	**5.8%**
Jakafi	**2,135**	**7.0%**
Xolair	2,112	3.0%
Remicade	2,020	0.0%
Botox	2,012	1.8%
Bamlanivimab	1,978	-5.4%
Hemlibra	1,973	2.5%
Actemra	1,915	1.1%
Jardiance	**1,901**	**4.9%**
Gardasil / 9	**1,881**	**5.9%**
Shingrix	**1,848**	**7.0%**
Tecentriq	1,835	3.0%
Otezla	**1,804**	**8.2%**
Tagrisso	1,780	1.0%
Latuda	**1,754**	**5.0%**
Vraylar	**1,728**	**3.5%**
Entresto	**1,712**	**7.0%**
Ranking†: 51-100		
Rituxan	1,687	0.0%
Tepezza	1,661	0.0%
Xeljanz	**1,648**	**4.9%**
Xifaxan	**1,644**	**7.9%**
Triumeq	**1,636**	**4.9%**
ProQuad/M-M-R II/Varivax	**1,630**	**6.8%**
Fluzone	**1,596**	**5.0%**
Taltz	**1,542**	**5.5%**
Perjeta	**1,539**	**4.5%**
Aubagio	**1,535**	**5.1%**
Neulasta	1,514	1.1%
Tremfya	**1,503**	**4.8%**
Lucentis	1,470	0.0%
Xgeva	**1,434**	**5.7%**
Gilenya	**1,427**	**5.1%**
Januvia	**1,404**	**4.9%**
Descovy	**1,397**	**4.8%**
Cimzia	**1,385**	**3.9%**
Activase/ TNKase	1,364	0.3%
Vimpat	**1,322**	**5.3%**
Sprycel	**1,297**	**4.4%**
Rinvoq	**1,271**	**7.4%**
Xyrem	**1,266**	**8.5%**
Yervoy	1,265	2.3%
Victoza	**1,258**	**4.9%**
Imfinzi	1,246	0.7%
Restasis	**1,234**	**5.0%**
Alimta	**1,234**	**3.8%**
Creon	**1,191**	**6.2%**
Trelegy Ellipta	**1,175**	**4.9%**
Opsumit	**1,147**	**4.8%**
Tysabri	**1,142**	**7.1%**
Simponi / Aria	**1,127**	**4.8%**
Calquence	1,089	0.0%
Lynparza	1,086	1.0%
Ingrezza	**1,083**	**4.7%**
Odefsey	**1,076**	**4.8%**
Uptravi	**1,056**	**4.8%**
Cabometyx	**1,054**	**7.5%**
Humalog / Mix	1,053	0.0%
Tivicay	**1,050**	**4.9%**
Lantus	1,008	0.0%
Linzess	**1,006**	**5.0%**
Novolog / Mix	1,005	0.0%
Avastin	1,002	0.0%
Benlysta	**1,000**	**4.2%**
Ultomiris	990	-2.0%
Rexulti	**971**	**6.7%**
Velcade	962	0.0%
Nucala	949	3.2%
Ranking†: 101-150		
Promacta	**947**	**7.1%**
Venclexta	**934**	**5.0%**
Lenvima	**913**	**5.2%**
Vyndaqel/ Vyndamax	910	0.1%
Abraxane	**898**	**4.5%**
Kadcyla	**884**	**4.5%**
Tasigna	**882**	**7.1%**
Sandostatin/ LAR	843	0.0%
Humulin / Mix	833	0.0%
Avonex	830	2.0%
Sotrovimab	828	i
Symbicort	**827**	**3.3%**
Mvasi	826	1.1%
Erleada	**813**	**4.8%**
Austedo	**803**	**5.9%**
Symtuza	**801**	**4.5%**
Jynarque	800	i
Esbriet	796	3.0%
Fasenra	**790**	**3.7%**
Synthroid	**767**	**4.9%**
Myrbetriq	765	3.0%
Bridion	**763**	**5.0%**
Saxenda	**762**	**4.0%**
Mavyret	754	0.0%
Kyprolis	**736**	**5.8%**
Brilinta	**736**	**5.1%**
Farxiga/Xigduo	**732**	**4.0%**
Lexiscan	717	1.5%
Prezista/ Prezcobix	**709**	**4.5%**
Takhzyro	703	3.0%
Herceptin	691	0.0%
Tecfidera	680	0.0%
Trintellix	**675**	**5.0%**
Breo Ellipta	671	2.2%
Adcetris	**670**	**7.8%**
Abilify Maintena	**670**	**4.8%**
Advair	668	0.7%
Rybelsus	**665**	**6.5%**
Strensiq	647	-1.3%
Rebif	**635**	**7.1%**
Janssen COVID-19 Vaccine	634	i
Molnupiravir	632	i
Fluarix/ FluLaval	**627**	**3.5%**
Tyvaso	608	2.3%
Tafinlar/ Mekinist	**606**	**5.6%**
Lupron	**604**	**12.6%**
Inlyta	**599**	**5.0%**
Epidiolex	594	0.0%
Tresiba	594	0.0%
Dovato	**589**	**4.9%**
Ranking†: 151 – 200		
Basaglar	588	0.0%
Spinraza	588	i
Verzenio	**582**	**6.7%**
Vascepa	**578**	**4.0%**
Copaxone	573	0.0%
Menactra	**573**	**5.0%**
Nplate	**566**	**5.9%**
Krystexxa	**565**	**4.8%**

Drug Name	Revenue†	Δ WAC‡
Repatha	**557**	**4.9%**
Ubrelvy	**552**	**5.0%**
Pneumovax 23	**547**	**6.9%**
Novoseven / RT	543	3.0%
Juluca	**540**	**4.9%**
Aranesp	537	0.0%
Xywav	535	-2.0%
Implanon/ Nexplanon	**533**	**5.8%**
Gattex	529	-21.6%
Premarin Family	**525**	**4.1%**
Afinitor/ Disperz	521	0.0%
Epogen	521	0.0%
Advate	517	3.0%
Exparel	**507**	**6.9%**
Eloctate	502	3.2%
Ninlaro	**501**	**5.3%**
Ilaris	501	2.0%
Injectafer	**495**	**5.2%**
Reblozyl	485	2.3%
Nuplazid	**484**	**9.1%**
Erbitux	**482**	**3.8%**
Kanjinti	479	1.2%
RotaTeq	**473**	**4.6%**
Zolgensma	469	0.1%
Nurtec ODT	**463**	**5.0%**
Fabrazyme	**462**	**5.0%**
Exondys 51	454	0.0%
Orkambi	451	0.0%
Ruxience	449	0.0%
Forteo	**442**	**5.4%**
Emgality	**435**	**4.4%**

Drug Name	Revenue†	Δ WAC‡
Xiaflex	**432**	**8.0%**
Lo Loestrin Fe	**423**	**5.0%**
Kalydeco	421	0.0%
Infanrix/ Pediarix	**417**	**8.0%**
Epclusa	412	0.0%
Vumerity	**410**	**3.9%**
Yescarta	406	i
Acthar	403	0.7%
Alecensa	398	3.0%
Evrysdi	397	-2.0%
Pulmozyme	395	0.0%
Ranking†: 201-250		
Remodulin	392	0.0%
Alprolix	388	3.1%
Inflectra	385	0.0%
Vemlidy	**384**	**4.8%**
Anoro Ellipta	382	3.0%
Flovent	378	2.9%
Boostrix	371	2.9%
Trodelvy	**370**	**4.2%**
Janumet / XR	**367**	**4.9%**
Kesimpta	363	1.0%
Cyramza	**358**	**3.8%**
Enhertu	358	2.3%
Bosulif	**354**	**5.0%**
Bexsero	**348**	**7.0%**
Vectibix	**347**	**5.8%**
Tradjenta	**347**	**4.9%**
Retacrit	344	0.0%
Vivitrol	**344**	**4.1%**
Suboxone Film	343	0.0%
Multaq	341	3.0%
Gazyva	340	3.0%

Drug Name	Revenue†	Δ WAC‡
Bendeka	340	0.0%
Padcev	**340**	**7.6%**
Kisqali	**339**	**7.1%**
Tukysa	**334**	**6.0%**
Myozyme/ Lumizyme	**334**	**3.8%**
Evenity	**331**	**5.5%**
Levemir	330	0.0%
Inomax	329	i
Udenyca	327	0.0%
Olumiant	**324**	**5.5%**
Pentacel	**323**	**3.5%**
Bydureon	**321**	**4.1%**
Lamictal/XR	**319**	**5.1%**
Truvada	314	0.0%
Aimovig	**313**	**5.8%**
Briviact	312	3.0%
Chantix	**309**	**3.9%**
Invokana/ Invokamet	**308**	**4.8%**
Libtayo	306	2.3%
Orenitram ER	**306**	**4.9%**
Wakix	**305**	**11.6%**
Trokendi XR	**305**	**6.0%**
Toujeo	303	0.0%
Jevtana	**296**	**5.0%**
Isentress	**294**	**5.0%**
Ravicti	**292**	**4.7%**
Zejula	**291**	**5.0%**
Venofer	**290**	**3.3%**
Risperdal Consta	**287**	**4.8%**

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 2021, in millions.

‡Four quarter WAC change.

§Bolding indicates the 149 drugs subset from the greater 250 that had a WAC price increase greater than medical CPI + 2%.

We then determined which of those drugs had a WAC price increase over the one-year period that exceeded the rate of medical consumer price index (CPI) + 2%. This was calculated as the difference between the average medical CPI using unadjusted rates, which was 1.23% for 2021 relative to 2020. The medical CPI is one of eight major components of the CPI recorded and reported by the US Bureau of Labor Statistics.[8] Medical CPI comprises medical care services (professional services, hospital and related services, and health insurance) and medical care commodities (medical drugs, equipment, and supplies).[9] Drugs whose WAC price percentage increases had not exceeded the rate of medical CPI + 2% (3.23%) 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.

We identified 149 drugs that met the WAC price increase greater than medical CPI + 2%, denoted in bolded italicized font in Table 2.1. Among those 149 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 over the period of 2020 to 2021. 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.

We then ranked those drugs whose net price increases had the largest positive impact on US spending over the prior year and we removed any drug where the increase in spending due to increase in net price was smaller than $25 million. To create the ranking, we used calculations by SSR Health that dollarized the impact of net price changes year-on-year to give a representative rank ordering of the size of the impact by product during 2021, driven by both size of the product (in terms of total net sales) and size of the net price impact.

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 and one added manual data quality flag by SSR Health, we arrived at the top 10 drugs derived from SSR Health based on their corrected increase in drug spending due to net price change. We note that for one product, Lupron®, we relied on an alternative data source to estimate the increase in drug spending due to net price change given manual data quality flags from SSR Health and correspondences with additional sources. The manufacturer of Lupron® did not provide corrected estimates.

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
Lupron® (Leuprolide)	1
Entyvio® (Vedolizumab)	2
Biktarvy® (Bictegravir/Emtricitabine/Tenofovir Alafenamide)	3
Cosentyx® (Secukinumab)	4
Xifaxan® (Rifaximin)	5
Invega Sustenna®/Trinza® (Paliperidone)	6
Vyvanse® (Lisdexamfetamine)	7
Genvoya® (Elvitegravir/Cobicistat/Emtricitabine/Tenofovir)	8
Tremfya® (Guselkumab)	9
Prolia® (Denosumab)	10
Promacta® (Eltrombopag)	11
Skyrizi® (Risankizumab)	12
Jakafi® (Ruxolitinib)	13
Symbicort® (Budesonide)	14
Rexulti® (Brexpiprazole)	15

*Medical care CPI was 1.23% in 2021.
†Prior to manufacturer revisions.

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 2020 compared with the average price in 2019 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 pegloticase, a patient or their optional supplemental insurer would be responsible for paying an average of $3,210 more per year based on the increase in unit price from 2019 to 2020. As with the main top 10 drugs, manufacturers also had a chance to review and comment on those net prices for the three Part B drugs. Pegloticase had previously been assessed for the 2019 to 2020 time period in the prior UPI report and found to have a net price increase unsupported by new clinical evidence. As such, under the UPI protocol, pegloticase is identified as having had an important list price increase for this time period but is not re-reviewed for supporting evidence.

Table 2.3 shows the 12 drugs that were chosen for assessment and one drug that was previously assessed for the same time period. 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)	2020 to 2021 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			
Xifaxan® (Rifaximin)	7.94%	12.14%	$174.7
Invega Sustenna®/Trinza® (Paliperidone)	4.83%	7.32%	$170.4
Prolia® (Denosumab)	5.79%	6.11%	$123.8
Entyvio® (Vedolizumab)	6.30%	4.50%	$118
Promacta® (Eltrombopag)	7.06%	11.46%	$94.9
Rexulti® (Brexpiprazole)	6.70%	7.61%	$67.9
Lupron® (Leuprolide)	6.20%	10.0%	$54.9
Drugs with Price Increases with New Clinical Evidence†			
Cosentyx® (Secukinumab)	7.05%	6.82%	$183.0
Tremfya® (Guselkumab)	4.81%	8.89%	$129.4
Jakafi® (Ruxolitinib)	7.01%	3.80%	$78.3
Part B Drugs with Price Increases Unsupported by New Clinical Evidence			
Drug (Generic)	**2019-2020 List Price Increase**	**Increase in Spending Due to Price Increase (Total Population, Per-patient§ (in Thousands)**	
Somatuline® Depot (Lanreotide)	11.20%	$33,000, $1.21	
Adcetris® (Brentuximab Vedotin)	9.23%	$14,000, $1.64	
Krystexxa® (Pegloticase)‡	11.78%	$13,800, $3.21	

WAC: wholesale acquisition cost

*Year-over-year percentage changes were estimated by averaging over the four quarterly changes in price (i.e., Q1 2020 to Q1 2021; Q2 2020 to Q2 2021; Q3 2020 to Q3 2021 and; Q4 2020 to Q4 2021).

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

‡Pegloticase had been previously assessed for the 2019 to 2020 time period in the prior UPI Report and was found to have a net price increase unsupported by new clinical evidence. As such, under the UPI Protocol, pegloticase is identified as having had an important list price increase for this time period but is not re-reviewed for supporting evidence.

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

3. Main List

3.1. Cosentyx® (Secukinumab, Novartis)

Introduction

Cosentyx® (secukinumab, Novartis) is a human interleukin-17a antagonist that was approved by the Food and Drug Administration (FDA) in 2015.[10] It is currently indicated for active psoriatic arthritis, active enthesitis-related arthritis, moderate-to-severe plaque psoriasis, active ankylosing spondylitis (adults only), and was most recently approved in 2020 for the treatment of active non-radiographic axial spondyloarthritis in adults. In 2021, the indications of psoriatic arthritis, enthesitis-related arthritis, and moderate-to-severe plaque psoriasis that were originally approved for adults were expanded to include pediatric patients.

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

- Active psoriatic arthritis
- Moderate-to-severe plaque psoriasis
- Active ankylosing spondylitis
- Active non-radiographic axial spondyloarthritis.

Price Increase

Over the 12 months (four quarters) for which price changes were assessed, the WAC for secukinumab increased by approximately 7.05%, while its estimated net price increased by 6.82%. This net price change over the assessed four quarters resulted in an estimated increase in drug spending of $183 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 secukinumab as of January 2020. Following that, we conducted an independent systematic literature review, limited to randomized controlled trials (RCT), over the 24 months review timeframe (January 2020 – December 2021) (see Tables N1 and N2 in Appendix N). In addition, we reviewed the RCT and non-RCT information that Novartis submitted to us to consider as new clinical information (51 references [21 conference presentations and 30 published manuscripts]). Of the 51 references submitted by the manufacturer, 16 articles were excluded because they did not meet our UPI review criteria. The primary reasons for excluding these studies are provided in Table 3.1. Following our systematic

literature review and the review of the remaining 35 articles submitted by the manufacturer, we identified six references related to three publications (PREVENT[11-13] and MAXIMISE[14-16]) that met our criteria of new and potentially moderate-to-high quality evidence on the benefits and/or harms of secukinumab. Additional details on these trials are provided below. The remaining 29 references submitted by the manufacturer presented previously known information about secukinumab or were considered low quality (Table 3.2).

Table 3.1. Studies Not Meeting UPI Review Criteria

Reason	Number of References
Study published outside of the timeframe of our review	5
Indication accounts for less than 10% of use	9
Outcomes not relevant to our 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 3.2. Studies Not Meeting Criteria for New Moderate- to High-Quality Evidence

Reasons	Number of References
Low-quality evidence	3
Previously known information about secukinumab related to safety	5
Previously known information about secukinumab related to efficacy	21

Table 3.3. Summary of New Evidence

Baseline Evidence (Before January 2020)	New Evidence
Secukinumab was indicated for moderate-to-severe plaque psoriasis, active psoriatic arthritis, active ankylosing spondylitis, and active enthesitis-related arthritis.	PREVENT is a Phase III RCT evaluating the efficacy and safety of secukinumab in patients with active non-radiographic axial spondyloarthritis.[11-13] Based on evidence from the PREVENT trial, the FDA granted approval for secukinumab for the treatment of active non-radiographic axial spondyloarthritis in adults in June 2020.[10]
Secukinumab was indicated for the treatment of active psoriatic arthritis. Axial involvement occurs in 25-70% of patients with psoriatic arthritis. Although the current practice has been to use TNF inhibitors for patients with axial psoriatic arthritis, there is no consensus on the management of this condition, and there was no RCT evidence supporting the efficacy of TNF inhibitors or any other biologic in this patient population.	MAXIMISE was a Phase III trial evaluating the efficacy and safety of secukinumab in patients with psoriatic arthritis with axial manifestations.[14-16] This is the first RCT to evaluate the efficacy of a biologic on axial manifestations in individuals with psoriatic arthritis.

FDA: Food and Drug Administration, RCT: randomized controlled trial, TNF: tumor necrosis factor

New Evidence

The **PREVENT** trial was a two-year Phase III RCT evaluating the efficacy and safety of secukinumab in patients with active non-radiographic axial spondyloarthritis completed in March 2021.[11-13] A peer-reviewed publication (Deodhar 2021) reports interim one-year results.[11] Patients were randomized 1:1:1 to receive either subcutaneous secukinumab 150 mg with a loading dose (LD arm) (n=185), secukinumab 150 mg without a loading dose (NL arm) (n=184), or placebo (n=186) once weekly for four weeks and then every four weeks thereafter. At week 20, patients were allowed to change their treatment to either open-label secukinumab or standard of care. The primary endpoint was at least a 40% improvement in Assessment of Spondyloarthritis International Society (ASAS40) at week 16 for the LD arm and week 52 for the NL arm. At week 16, ASAS40 was higher in both secukinumab arms versus placebo (42.2% and 41.5% vs. 29.2%; P<0.05). Similarly, despite 64% of placebo patients (and about 50% of secukinumab patients) switching to open-label treatment prior to one year, more patients achieved ASAS40 response in the secukinumab arm versus placebo (39.8% and 35.4% vs. 19.9%; P<0.05) at week 52. Two-year results from a conference abstract (Poddubnyy 2021)[12] showed that secukinumab had sustained improvement, with no new safety signals identified.

The **MAXIMISE** trial was a Phase III multicenter RCT that evaluated the efficacy of secukinumab in individuals with axial manifestations of psoriatic arthritis who had used at least two non-steroidal anti-inflammatory drugs.[14-16] Patients were randomized 1:1:1 to receive either secukinumab 300 mg (n=167), secukinumab 150 mg (n=165), or placebo (n=166) once weekly for four weeks and then every four weeks thereafter. Re-randomization occurred at week 12, where patients originally in the placebo arm were randomized to either secukinumab 150 mg or 300 mg. The primary outcome was at least a 20% improvement in ASAS20 in the secukinumab 300 mg arm at week 12. More patients in the secukinumab arms (300 mg: 63%; 150 mg: 66%) experienced an ASAS20 response at week 12 compared to the placebo arm (31%; p<0.001). In addition, secukinumab was superior to placebo on other secondary outcomes. The benefits were maintained through week 52.

Rating of New Evidence (Quality and Magnitude)

The PREVENT trial provides high-quality evidence of a substantial benefit of treatment with secukinumab for patients with non-radiographic spondylarthritis.

The MAXIMISE trial provides high-quality evidence that secukinumab improves axial symptoms in patients with psoriatic arthritis who have such symptoms.

Conclusion

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

3.2. Xifaxan® (Rifaximin, Bausch Health)

Introduction

Xifaxan® (rifaximin, Bausch Health) is a rifamycin antibacterial drug originally approved by the FDA in 2004.[17] It is indicated for the 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.[17]

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 7.94%, while its estimated net price increased by 12.14%. This net price change over the assessed four quarters resulted in an estimated increase in drug spending of $175 million. All pricing information was obtained from SSR Health. The manufacturer disputed the net price and budget impact findings from SSR Health but did not provide corrected estimates.

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 2020. Following that, we conducted an independent systematic literature review, limited to RCTs, over the 24 months review timeframe (January 2020 – December 2021) (see Tables N1 and N2 in Appendix N). Bausch Health did not submit any references to be considered for our review. Our literature search identified 18 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.

Conclusion

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

3.3. Invega Sustenna®/Invega Trinza® (Paliperidone, Janssen)

Introduction

Invega Sustenna® (paliperidone palmitate) and Invega Trinza® (paliperidone palmitate) are long-acting injectable preparations (of the same antipsychotic medication) that were first approved by the FDA in 2006.[18,19] Invega Sustenna® is a one-month extended-release injection approved in adults to treat schizophrenia, schizoaffective disorder, and is used as an adjunct to mood stabilizers or antidepressants.[18] Invega Trinza® is a three-month injection specifically indicated for the treatment of schizophrenia after patients have been adequately treated with Invega Sustenna® for at least four months.[19] 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 paliperidone increased by approximately 4.83%, while its estimated net price increased by 7.32%. This net price change over the assessed four quarters resulted in an estimated increase in drug spending of $170 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 paliperidone 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 Tables N1 and N2 in Appendix N). Janssen did not submit any references to be considered for our review. Our literature search identified eight articles, none of which met our inclusion criteria of new and potentially moderate-to-high quality evidence on the benefits and/or harms of paliperidone.

Conclusion

After careful review of the evidence, we conclude that paliperidone (Invega Sustenna®/Invega Trinza®) had a price increase unsupported by new clinical evidence.

3.4. Tremfya® (Guselkumab, Janssen)

Introduction

Tremfya® (guselkumab, Janssen) is an interleukin-23 blocker approved by the FDA in 2017.[20] It was originally approved for the treatment of moderate-to-severe plaque psoriasis in individuals who are candidates for systemic therapy or phototherapy. Most recently, it was approved for active psoriatic arthritis in July 2020. Based on market research, both 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 guselkumab increased by approximately 4.81%, while its estimated net price increased by 8.89%. This net price change over the assessed four quarters resulted in an estimated increase in drug spending of $129 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 guselkumab 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 Tables N1 and N2 in Appendix N). Janssen did not submit any references to be considered for our review. Our literature search identified seven articles, three of which met our inclusion criteria of new and potentially moderate- to high-quality evidence on the benefits and/or harms of guselkumab. Additional details on these trials are provided below.

Table 3.4. Summary of New Evidence

Baseline Evidence (Before January 2020)	New Evidence
Guselkumab was originally approved in 2017 for the treatment of moderate-to-severe plaque psoriasis in patients who are candidates for systemic therapy or phototherapy.	The **DISCOVER-1** trial was an RCT that evaluated the efficacy and safety of guselkumab in patients with active psoriatic arthritis who were biologic-naïve or had received TNF inhibitor treatment.[21] The **DISCOVER-2** trial was an RCT that evaluated the efficacy and safety of guselkumab in biologic-naïve patients with active psoriatic arthritis.[22] Based on the evidence from the Phase II trial[23] and the **DISCOVER 1 and 2** Phase III trials, the FDA granted approval for guselkumab for the treatment of active psoriatic arthritis.

FDA: Food and Drug Administration, RCT: randomized controlled trial, TNF: tumor necrosis factor

New Evidence

The **DISCOVER-1** trial was a Phase III multicenter RCT conducted in adult patients with active psoriatic arthritis who were either biologic-naïve or had previous treatment with a TNF inhibitor. Patients were randomized 1:1:1 to receive either subcutaneous guselkumab 100 mg every four weeks (n=128), guselkumab 100 mg at weeks zero and four and then every eight weeks (n=127), or placebo (n=126). Of the 381 patients who were randomized, 362 continued treatment for 24 weeks. The primary endpoint of the American College of Rheumatology 20% improvement (ACR20) at week 24 was met by more patients receiving guselkumab every four weeks and every eight weeks compared to those receiving placebo (59% and 52% vs. 22%, respectively). Similar responses were seen on other outcomes, regardless of prior TNF inhibitor use. In addition, rates of serious adverse events were low and similar across groups.

The **DISCOVER-2** trial was a Phase III multicenter RCT conducted in adult patients with active psoriatic arthritis who were biologic-naïve. Patients were randomized 1:1:1 to receive either subcutaneous guselkumab 100 mg every four weeks (n=246), guselkumab at weeks zero and four and then every eight weeks (n=248), or placebo (n=247). Of the 739 patients who were randomized, 716 patients continued treatment for 24 weeks. The primary endpoint of ACR20 at week 24 was met by more patients receiving guselkumab every four weeks and every eight weeks compared to those receiving placebo (64% and 64% vs. 33%, respectively). Similar responses were seen on other outcomes. In addition, rates of serious adverse events were low and similar across groups.

Rating of New Evidence (Quality and Magnitude)

In combination, **DISCOVER-1 and DISCOVER-2** trials provide high-quality evidence on the use of guselkumab in active psoriatic arthritis. Evidence from these trials showed substantial and statistically significant improvement in joint symptoms, physical functions, and health-related quality of life in favor of guselkumab compared to placebo. Therefore, we conclude that these trials provide high-quality evidence of a substantial net benefit for guselkumab compared with what was previously known.

Conclusion

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

3.5. 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. 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 5.79%, while its estimated net price increased by 6.11%. This net price change over the assessed four quarters resulted in an estimated increase in drug spending of $124 million. All pricing information was obtained from SSR Health. The manufacturer disputed the net price and budget impact findings from SSR Health but did not provide corrected estimates. Finally, the manufacturer noted that drugs that we did not include in net price vetting with manufacturers may have had higher estimated increases in drug spending due to net price changes than our finalized and corrected list. This study design feature of limiting our initial list to the top 15 drugs per SSR Health data will be noted elsewhere in the report.

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 2020. Following that, we conducted an independent systematic literature review, limited to RCTs, over the 24 months review timeframe (January 2020 – December 2021) (see Tables N1 and N2 in Appendix N). In addition, we reviewed the RCT and non-RCT information that Amgen submitted to us to consider as new clinical information (four references [three conference presentations and one published manuscript]). Following our systematic literature review (Tables N1 and N2, Appendix N) and the review of the four articles submitted by the manufacturer, we identified one reference related to one study (Singer 2021) that met our criteria of new and potentially moderate- to high-quality evidence on the benefits and/or harms of denosumab. Additional details on this trial are provided below. The remaining three references submitted by the manufacturer were published outside the timeframe of our review (see Table 3.5).

Table 3.5. Studies Not Meeting UPI Review Criteria

Reason	Number of References
Study published outside the timeframe of our review	3

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

Table 3.6. Summary of New Evidence

Baseline Evidence (Before January 2020)	New Evidence
Prior studies had demonstrated higher long-term persistence with denosumab than had been seen in other studies that looked at persistence with oral bisphosphonates.[24,25] However, the magnitude of the difference as well as the comparison being made across different studies would have led us to consider the information as low-quality evidence even of greater persistence with denosumab than oral bisphosphonates. Thus, a study showing moderate- or high-quality evidence of greater persistence would be new evidence.	**Singer 2021** was a retrospective cohort study that evaluated the long-term persistence of denosumab vs. oral/intravenous bisphosphonate among postmenopausal women with osteoporosis.

New Evidence

Singer 2021 was a retrospective cohort study utilizing administrative claims data to assess long-term persistence among postmenopausal women with osteoporosis who have initiated anti-resorptive therapies. The study included women who had initiated either denosumab (n=145,056), oral (n=318,419), or intravenous bisphosphonate (n=48,066) or raloxifene (n=31,400) and had greater than one year of coverage at baseline between the years of 2011 and 2014. Treatment persistence declined over time for all patients; however, in patients with at least 36 months of follow-up, persistence was consistently higher among those on denosumab compared to oral bisphosphonate for up to three years (year one: 73% vs. 39%, year two: 50% vs. 25%, year three: 38% vs. 17%). Persistence was also much higher with denosumab than with intravenous bisphosphonate.

Rating of New Evidence (Quality and Magnitude)

Based on the magnitude of the effect, this study provides moderate-quality evidence of greater persistence with denosumab than with oral bisphosphonates. This, however, is indirect evidence of patient benefit. The relative effect of denosumab compared with oral bisphosphonates on patient-important outcomes, including prevention of fragility fractures and harms, is uncertain, requiring further rating down the evidence for indirectness. As such, although this is a close call, this study provides only low-quality evidence of improvement in patient-important outcomes with denosumab versus oral bisphosphonates compared with what was previously known.

Conclusion

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

3.6. Entyvio® (Vedolizumab, Takeda)

Introduction

Entyvio® (vedolizumab, Takeda) is a humanized monoclonal antibody that was approved by the FDA in 2014 for the treatment of adults with moderate-to-severe ulcerative colitis and moderate-to-severe Crohn's disease.[26] Based on clinical input, both 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 vedolizumab increased by approximately 6.30%, while its estimated net price increased by 4.50%. This net price change over the assessed four quarters resulted in an estimated increase in drug spending of $118 million. All pricing information was provided by the manufacturer after a review of the SSR Health data.

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 vedolizumab 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 Tables N1 and N2 in Appendix N). In addition, we reviewed the RCT and non-RCT information that Takeda submitted to us to consider as new clinical information (22 references [six conference presentations and 16 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 vedolizumab (Table F1, Appendix F). Of the 22 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 3.7. Of the remaining 15 articles, 14 presented previously known information about vedolizumab, while the remaining study presented new evidence of no clinical improvement versus a comparator agent (see Table 3.8). As an example, we highlighted the EARNEST trial (Travis et al. 2021) that did not meet the UPI criteria.[27]

Table 3.7. Studies Not Meeting UPI Review Criteria

Reason	Number of References
Study published outside of the timeframe of our review	1
Indication accounts for less than 10% of use	1
Outcomes not relevant to our scope	4
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 3.8. Studies Not Meeting Criteria for New Moderate- to High-Quality Evidence

Reason	Number of References
Previously known information about vedolizumab related to efficacy	10
Previously known information about vedolizumab related to safety	4
(New) evidence of no clinical improvement with vedolizumab	1

Study Not Meeting UPI Review Criteria

The **EARNEST trial** was a Phase IV RCT that evaluated the efficacy and safety of vedolizumab in adult patients with active chronic pouchitis who have had three or more recurrent episodes within one year of screening.[27] Patients were randomized to receive either intravenous vedolizumab (n=51) or placebo (n=51) for 30 weeks; all patients also received four weeks of ciprofloxacin. Treatment with vedolizumab resulted in greater clinical remission rates at week 14 than that of placebo (31.4% vs. 9.8%, p=0.013); its superiority over placebo was maintained at week 34 (p=0.043). Safety results were consistent with previously known evidence of vedolizumab treatment.

Reason for Not Meeting UPI Review Criteria

Pouchitis is a complication among patients with ulcerative colitis who have undergone proctocolectomy with ileal pouch anal anastomosis surgery.[28] For a subset of patients, pouchitis does not resolve with antibiotic therapy and becomes a chronic condition. Although previous case series have demonstrated the benefit of vedolizumab in patients with chronic pouchitis, this is the first RCT of vedolizumab that evaluates its use in this patient population. Based on the results from the EARNEST trial, the European Medicines Agency approved vedolizumab for the treatment of active chronic pouchitis in patients who have had an inadequate response to or lost response to antibiotic therapy. Vedolizumab is currently not approved for the treatment of chronic pouchitis in the US, and it is unclear if the company will be seeking approval for this indication in the US in the future. However, given how closely related chronic pouchitis is to ulcerative colitis, we evaluated this study as potential new evidence on the use of vedolizumab. Based on manufacturer input, we are uncertain whether the use in chronic pouchitis accounts for at least 10% of the use of vedolizumab; our review and clinical input suggest it is unlikely for chronic pouchitis to account for at least 10% of vedolizumab's use.

Conclusion

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

3.7. Promacta® (Eltrombopag, Novartis)

Introduction

Promacta® (eltrombopag, Novartis) is a small molecule thrombopoietin receptor agonist that was approved by the FDA in 2008.[29] It is currently indicated for the treatment of thrombocytopenia in patients who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy and patients with chronic hepatitis C.[29] Eltrombopag is also approved for the treatment of severe aplastic anemia in patients who have had an insufficient response to immunosuppressive 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 eltrombopag increased by approximately 7.06%, while its estimated net price increased by 11.46%. This net price change over the assessed four quarters resulted in an estimated increase in drug spending of $95 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 eltrombopag 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 Tables N1 and N2 in Appendix N). Novartis did not submit any references to be considered for our review. Our literature search identified seven articles, none of which met our inclusion criteria of new and potentially moderate- to high-quality evidence on the benefits and/or harms of eltrombopag.

Conclusion

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

3.8. Jakafi® (Ruxolitinib, Incyte)

Introduction

Jakafi® (ruxolitinib, Incyte) is a kinase inhibitor approved by the FDA in 2011.[30] 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 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 7.01%, while its estimated net price increased by 3.80%. This net price change over the assessed four quarters resulted in an estimated increase in drug spending of $78 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 ruxolitinib 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 Tables N1 and N2 in Appendix N). In addition, we reviewed the RCT and non-RCT information that Incyte submitted to us to consider as new clinical information (eight references [two conference presentations and six published manuscripts]). We identified two references (REACH-2[31] and REACH-3[32]) 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 3.10). Of the remaining six references, three articles were excluded because they were considered to be previously known information, while the remaining three articles were considered low quality (see Table 3.9).

Table 3.9. Studies Not Meeting Criteria for New Moderate- to High-Quality Evidence

Reasons	Number of References
Previously known information about ruxolitinib related to efficacy	3
Low-quality study	3

Table 3.10. Summary of New Evidence

Baseline Evidence (Before January 2020)	New Evidence
Based on a single-arm open-label trial, ruxolitinib gained FDA approval for steroid-refractory acute graft-vs.-host disease in patients 12 years and older in 2019.	**REACH-2** was an RCT that evaluated the efficacy and safety of ruxolitinib compared to the investigator's choice of nine commonly used standard of care options in patients with glucocorticoid-refractory acute graft-vs.-host-disease after allogeneic stem-cell transplantation.[31] This trial demonstrated superior efficacy and modest toxicity of ruxolitinib compared to other standard care agents. In addition, based on this trial, ruxolitinib was upgraded from a category 2A recommendation to a category 1 treatment option for acute graft-vs.-host disease in the National Comprehensive Cancer Network guideline.
Prior to September 2021, ruxolitinib was not indicated for individuals with chronic graft-vs.-host disease.	The **REACH-3** 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.[32] 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 **REACH-2** study was a Phase III open-label multicenter RCT that enrolled adolescent and adult patients 12 years and older with glucocorticoid-refractory acute graft-versus-host disease after allogeneic stem-cell transplantation.[31] Patients were randomized to receive either oral ruxolitinib 10 mg twice daily (n=154) or the investigator's choice of nine commonly used therapies (n=155), stratified by baseline grade (II-IV) of disease. The primary endpoint of overall response at day 28 was higher in the ruxolitinib arm compared to the control arm (62% vs. 39%; odds ratio: 2.64; P<0.001). The superiority of ruxolitinib on overall response was maintained at day 56 (44% vs. 22%; odds ratio: 2.38; P<0.001). Ruxolitinib was also associated with longer median failure-free survival (five months vs. one month; hazard ratio: 0.46; 95% CI, 0.35 to 0.60). However, the follow-up duration was insufficient to draw conclusions about survival benefits. At the time of the analysis, although the overall survival was longer in the ruxolitinib arm (11.1 months) compared to the control arm (6.5 months), statistical significance was not reached (hazard ratio: 0.83; 95% CI: 0.60-1.15). Thrombocytopenia (33%), anemia (30%), and cytomegalovirus infection (26%) were the most

commonly reported safety events in the ruxolitinib arm; there was no difference in frequency of anemia and cytomegalovirus infections compared to the control group.

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.[32] 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 long 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 REACH-2, ruxolitinib was approved for steroid-refractory acute graft-versus-host disease based on a single-arm trial. However, REACH-2 provides new evidence on the efficacy and safety of ruxolitinib compared to other commonly used therapies in this population. Evidence from this trial indicates ruxolitinib was superior to other commonly used therapies on overall response rate, with modest toxicity. The trial was open label, providing moderate-quality evidence of a substantial benefit for ruxolitinib versus other commonly used therapies in glucocorticoid-refractory acute graft-versus-host-disease.

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.

Conclusion

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

3.9. Rexulti® (Brexpiprazole, Otsuka)

Introduction

Rexulti® (brexpiprazole, Otsuka) is an atypical antipsychotic indicated for the adjunctive treatment of major depressive disorder in adults and for the treatment of schizophrenia in adults and adolescents. Brexpiprazole was FDA-approved for both indications in 2015 and received expanded approval for adolescents (ages 13-17) with schizophrenia in 2021. 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 brexpiprazole increased by approximately 6.70%, while its estimated net price increased by 7.61%. This net price change over the assessed four quarters resulted in an estimated increase in drug spending of $68 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 brexpiprazole 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 Tables N1 and N2 in Appendix N). In addition, we reviewed the RCT and non-RCT information that Otsuka submitted to us to consider as new clinical information (15 references [three conference presentations and 12 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 brexpiprazole. Of the 15 references submitted by the manufacturer, two duplicates were excluded, while 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. Of the remaining six articles, one presented previously known information about brexpiprazole, while the remaining five studies were considered low quality (Table 3.12).

Table 3.11. Studies Not Meeting UPI Review Criteria

Reason	Number of References
Study published outside of the timeframe of our review	6
Indication accounts for less than 10% of use	1

*Two references were identified as duplicate submissions and not included above.
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
Low-quality evidence	5
Previously known information about brexpiprazole related to efficacy	1

Study Not Meeting UPI Review Criteria

Dragheim et al. 2021 presented the interim analyses of an ongoing single-arm open-label study conducted in adolescent patients with schizophrenia (n=167).[33] The trial was designed to assess the frequency and severity of adverse events of maintenance treatment with brexpiprazole in adolescents with schizophrenia. The interim analysis was conducted after about 100 patients had been on brexpiprazole for six months or longer. Of the 167 patients, 56.7% had treatment-emergent adverse events, 1.2% had severe treatment-emergent adverse events, 3% had serious treatment-emergent adverse events, and 1.2% had treatment-emergent adverse events that led to study discontinuation. The most common adverse events were somnolence, headache, and weight gain, which are consistent with the safety profile of brexpiprazole in adult patients.

Reason for Not Meeting UPI Review Criteria

The interim analysis presented by Dragheim et al. represents new data on the safety of brexpiprazole in adolescent patients with schizophrenia. However, based on manufacturer input, it is unlikely that use in adolescent patients with schizophrenia accounts for at least 10% of the overall utilization of brexpiprazole given that only about 1.4% of prevalent cases of diagnosed schizophrenia are in adolescents.[34]

Conclusion

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

3.10. Lupron® (Leuprolide, AbbVie)

Introduction

Lupron® (leuprolide acetate, AbbVie) is a gonadotropin-releasing hormone agonist originally approved by the FDA in 1985.[35] It is indicated for the treatment of advanced prostate cancer, for the management of endometriosis (including pain relief and reduction of endometriotic lesions), and for concomitant use with iron therapy for preoperative hematologic improvement in women with anemia caused by fibroids for whom three months of hormonal suppression is deemed necessary.[35] Leuprolide acetate is also approved for the treatment of pediatric patients with central precocious puberty.[35] 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 leuprolide increased by approximately 6.20%, while its estimated net price increased by 10.0%. This net price change over the assessed four quarters resulted in an estimated increase in drug spending of $55 million. Pricing information was obtained from SSR Health for WAC, while net pricing and budget impact was estimated based on IQVIA data alongside correspondences with the manufacturer. The manufacturer did not provide corrected estimates.

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 leuprolide 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 Tables N1 and N2 in Appendix N). In addition, we reviewed the RCT and non-RCT information that AbbVie submitted to us to consider as new clinical information (three references [three published manuscripts]). Of the three references submitted by the manufacturer, two articles were excluded and considered low-quality evidence (see Table 3.14). The third reference (Lopes 2021) met our criteria of new and potentially moderate- to high-quality evidence on the benefits and/or harms of leuprolide. Additional details on this trial are provided below.

Table 3.14. Studies Not Meeting Criteria for New Moderate- to High-Quality Evidence

Reasons	Number of References
Low-quality evidence	2

Table 3.15. Summary of New Evidence

Baseline Evidence (Before January 2020)	New Evidence
There are conflicting data about the cardiovascular safety of gonadotropin-releasing hormone agonists compared with gonadotropin-releasing hormone antagonists.[36-38] No trial has compared the cardiovascular risk between leuprolide and degarelix.	The **PRONOUNCE** study was a Phase III RCT conducted to compare the cardiovascular risk of a gonadotropin-releasing hormone antagonist, leuprolide, in patients with prostate cancer, with a gonadotropin-releasing hormone antagonist, degarelix.[39] No difference in cardiovascular events was found between degarelix and leuprolide. Cardiovascular safety among gonadotropin-releasing hormone antagonists and agonists remains unclear.

RCT: randomized controlled trial

New Evidence

The **PRONOUNCE** study was a Phase III multicenter RCT that enrolled male patients with prostate cancer and atherosclerotic cardiovascular disease.[39] A total of 545 patients were randomized 1:1 to receive a 240 mg loading dose of degarelix followed by 80 mg injections once a month for 11 doses or 22.5 mg leuprolide every 84 days for four doses. The primary outcome was time to the first major adverse cardiovascular event (MACE), which includes a composite of either stroke, myocardial infarction, or death. No difference in MACE was observed (5.5% in the degarelix arm vs. 4.1% in leuprolide arm; hazard ratio: 1.28; 95% CI: 0.59, 2.79; P=0.53). Due to slow enrollment and a low number of MACE events, this study was terminated early, with the investigators concluding that cardiovascular safety among gonadotropin-releasing hormone antagonists (degarelix) and agonists (leuprolide) remains uncertain.

Rating of New Evidence (Quality and Magnitude)

Although PRONOUNCE was a well-conducted RCT, it was terminated early, and it did not provide a clear answer to the question it was intended to answer. As such, it does not provide new evidence of substantial improvement in benefit compared with what was previously believed.

Conclusion

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

4. Medicare Part B List

4.1. Somatuline® Depot (Lanreotide, Ipsen)

Introduction

Somatuline® Depot (lanreotide, Ipsen) is a somatostatin analog injection that was first approved by the FDA for the treatment of acromegaly in 2007.[40] Lanreotide was subsequently approved for the treatment of adult patients with unresectable, well- or moderately-differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) and adult patients with carcinoid syndrome. Based on the information provided by the manufacturer, the treatment of GEP-NETs and carcinoid syndrome account for greater than 10% of lanreotide's use.

Price Increase

Over the 12 months (four quarters) for which price changes were assessed, the change in spending per unit of lanreotide increased by approximately 11.20%. The change in unit price over the assessed four quarters resulted in an estimated increase in drug spending by Medicare payers and patients of $33 million. Assuming up to 20% coinsurance, on average the change in unit price alone would result in up to $1,210 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 lanreotide as of January 2019. Following that, we conducted an independent systematic literature review, limited to RCTs, over the 24-month review timeframe (January 2019 – December 2020) (see Tables N1 and N2 in Appendix N). In addition, we reviewed the RCT and non-RCT information that Ipsen submitted to us to consider as new clinical information (16 references [14 conference presentations and two 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 lanreotide (Table K1, Appendix K). Of the 16 references submitted by the manufacturer, 11 articles were excluded because they did not meet our UPI review criteria, while the remaining five articles were considered low quality (see Tables 4.1 and 4.2). As an example, we highlighted one of the submitted articles (Cheung et al. 2020) that we classified as low-quality evidence.

Table 4.1. Studies Not Meeting UPI Review Criteria

Reason	Number of References
Study published outside of the timeframe of our review	6
Study population outside approved label indication	1
Outcomes not relevant to our scope	4

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

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

Reasons	Number of References
Low-quality evidence	5

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

Cheung et al. 2020[41] was a Canadian commercial claims database analysis of 908 patients who had been dispensed a prescription for lanreotide 120 mg (n=375) or octreotide 30 mg (n=533) between September 2015 and June 2018. The two somatostatin analogs were compared to one another on the following outcomes: injection burden, rescue medication use, and costs over the 12-month period from the first prescription. Patients treated with lanreotide experienced a lower injection burden (weighted average, 12.54 vs. 13.44 injections per patient; p<0.0001), lower mean use of rescue medication (0.01 vs. 0.05 claims per patient per year; p<0.05) as well as a lower mean total annual cost of medication ($27,829.35 per patient vs. $31,255.49 per patient; p<.0001).

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

This study directly compared lanreotide with another long-acting somatostatin analog (octreotide) commonly used in clinical practice and showed evidence in favor of lanreotide on the outcomes evaluated. However, using GRADE criteria, evidence from Cheung et al. 2020 is considered low quality in the absence of specific criteria that would increase the quality of evidence.

Conclusion

After careful review of the evidence, we conclude that lanreotide (Somatuline® Depot) had a price increase unsupported by new clinical evidence.

4.2. Adcetris® (Brentuximab Vedotin, Seagen)

Introduction

Adcetris® (brentuximab vedotin, Seagen) is a monoclonal antibody that was first approved by the FDA in 2011. It is indicated for the following conditions:

- Previously untreated Stage III or IV classical Hodgkin lymphoma, in combination with doxorubicin, vinblastine, and dacarbazine
- Classical Hodgkin lymphoma at high risk of relapse or progression as post-autologous hematopoietic stem cell transplantation (auto-HSCT) consolidation
- Classical Hodgkin lymphoma after the failure of auto-HSCT or after the failure of at least two prior multi-agent chemotherapy regimens in patients who are not auto-HSCT candidates
- Previously untreated systemic anaplastic large cell lymphoma or other CD30-expressing peripheral T-cell lymphomas, in combination with cyclophosphamide, doxorubicin, and prednisone
- Systemic anaplastic large cell lymphoma after the failure of at least one prior multi-agent chemotherapy regimen
- Primary cutaneous anaplastic large cell lymphoma or CD30-expressing mycosis fungoides who have received prior systemic therapy.

Based on the information provided by the manufacturer, all indications account for greater than 10% of brentuximab vedotin's use.

Price Increase

Over the 12 months (four quarters) for which price changes were assessed, the change in spending per unit of brentuximab vedotin increased by approximately 9.23%. The change in unit price over the assessed four quarters resulted in an estimated increase in drug spending by Medicare payers and patients of $14.0 million. Assuming up to 20% coinsurance, on average the change in unit price alone would result in up to $1,640 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 brentuximab vedotin as of January 2019. Following that, we conducted an independent systematic literature review, limited to RCTs, over the 24 months review timeframe (January 2019 – December 2020) (see Tables N1 and N2 in Appendix N). In addition, we reviewed the RCT and non-RCT information that Seagen submitted to

us to consider as new clinical information (21 references [10 conference presentations 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 brentuximab vedotin (Table J1, Appendix J). Of the 21 references submitted by the manufacturer, five articles were excluded because they did not meet our UPI review criteria, 10 presented previously known information about brentuximab vedotin, while the remaining six studies were considered low quality (see Tables 4.3 and 4.4). As an example, we highlighted three references related to one RCT (ECHELON-2) that reported on previously known information about brentuximab vedotin.

Table 4.3. Studies Not Meeting UPI Review Criteria

Reason	Number of References
Study published outside of the timeframe of our review	4
Indication accounts for less than 10% of use	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 4.4. Studies Not Meeting Criteria for New Moderate- to High-Quality Evidence

Reason	Number of References
Low-quality evidence	6
Previously known information about brentuximab vedotin related to efficacy	10

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

ECHELON-2 was a randomized, active-comparator trial conducted in patients with previously untreated CD30-positive peripheral T-cell lymphoma.[42-44] Patients were randomized 1:1 (n=226 each arm) to receive either brentuximab vedotin plus cyclophosphamide, doxorubicin, and prednisone (A+CHP) versus the standard-of-care combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). Patients treated with A+CHP had a longer median progression-free survival than those treated with CHOP (48.2 months vs. 20.8 months; hazard ratio 0.71, 95% CI: 0.54-0.93). In addition, the five-year progression-free survival rates (51.4% vs. 43%; hazard ratio: 0.70; 95% CI: 0.53, 0.91) and five-year overall survival rates (70.1% vs. 61%; hazard ratio: 0.72; 95% CI: 0.53, 0.99) were superior for A+CHP compared to CHOP.[43] The incidence of febrile neutropenia and peripheral neuropathy was similar between both treatment groups.

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

ECHELON-2 represents high-quality evidence assessing the benefit of brentuximab vedotin in combination with CHP versus CHOP in patients with previously untreated CD30-positive peripheral T-cell lymphoma. As indicated in the UPI protocol, ICER is looking for new evidence that shows substantial new benefits compared with what was previously believed before our review timeline of January 2019 – December 2020. The results from the ECHELON-2 trial were publicly announced in 2018, and it served as the basis for the FDA approval of brentuximab vedotin for the treatment of

CD30-positive peripheral T-cell lymphoma in November 2018.[45,46] Thus, the subsequent references of ECHELON-2 that fall into our review timeframe of January 2019 – December 2020 are considered previously known information on the efficacy and safety of brentuximab vedotin for the treatment of CD30-positive peripheral T-cell lymphoma.

Conclusion

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

4.3. Krystexxa® (Pegloticase, Horizon Therapeutics)

Introduction

Krystexxa® (pegloticase, Horizon Therapeutics) is a PEGylated uric acid specific enzyme approved by the FDA in 2010 for the treatment of chronic gout in adult patients refractory to conventional therapy.[47]

Price Increase

Over the 12 months (four quarters) for which price changes were assessed, the change in spending per unit of pegloticase increased by approximately 11.78%. The change in unit price over the assessed four quarters resulted in an estimated increase in drug spending by Medicare payers and patients of $13.8 million. Assuming up to 20% coinsurance, on average the change in unit price alone would result in up to $3,210 per year in additional payments by the patient. All pricing information was obtained from the Medicare Part B US government data source.

As noted above, the prior UPI report (looking at this same time period) concluded that pegloticase (Krystexxa®) had a net price increase unsupported by new clinical evidence, and so pegloticase was not re-reviewed as part of this report.

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APPENDIX

Appendix A. Cosentyx®

Appendix Table A1. References Submitted by Novartis

Citation	Decision
Magnolo N, et al. Efficacy and safety of secukinumab in enthesitis-related arthritis and juvenile psotriatic arthritis: primary results from a randomised, double-blind, placebo controlled, treatment withdrawal, phase 3 study (JUNIPERA). Ann Rheum Disease 2021.	Indication accounts for less than 10% of use
Gottlieb AB, et al. Sustained efficacy of secukinumab in patients with moderate-to-severe palmoplantar psoriasis: 2·5-year results from GESTURE, a randomized, double-blind, placebo-controlled trial. Br J Dermatol 2020.	Indication accounts for less than 10% of use
Reich K, et al. Secukinumab shows high and sustained efficacy in nail psoriasis: 2.5-year results from the randomized placebo-controlled TRANSFIGURE study. Br J Dermatol 2021.	Indication accounts for less than 10% of use
Mrowietz U, et al. Efficacy and safety of secukinumab in moderate to severe palmoplantar pustular psoriasis over 148 weeks: Extension of the 2PRECISE study. J Am Acad Dermatol 2021.	Indication accounts for less than 10% of use
Behren F, et al. Efficacy and Safety of Secukinumab in Patients with Spondyloarthritis and Enthesitis at the Achilles Tendon: 52-weeks Results from a Randomized, Placebo-controlled Phase 3b Trial. Arthritis Rheum 2020.	Indication accounts for less than 10% of use
Baraliakos X, et al. Magnetic resonance imaging characteristics in patients with spondyloarthritis and clinical diagnosis of heel enthesitis: post hoc analysis from the phase 3 ACHILLES trial. Arthritis Res Ther 2020.	Indication accounts for less than 10% of use
Bodemer C, Kaszuba A, Kingo K, et al. Secukinumab demonstrates high efficacy and a favourable safety profile in paediatric patients with severe chronic plaque psoriasis: 52-week results from a Phase 3 double-blind randomized, controlled trial. *J Eur Acad Dermatol Venereol.* 2021;35(4):938-947.	Indication accounts for less than 10% of use
Bodemer C, Kaszuba A, Kingo K, et al. Secukinumab demonstrated high efficacy and a favorable safety profile in pediatric patients with severe chronic plaque psoriasis: One-year results. 2020; 29th European Academy of Dermatolgoy and Venereology (EADV) Congress, Virtual Meeting.	Indication accounts for less than 10% of use
Bodemer C, Kaszuba A, Kingo K, et al. Secukinumab efficacy and safety profile in pediatric patients with severe chronic plaque psoriasis up to one year. Paper presented at: American Academy of Dermatology (AAD) Virtual Meeting Experience 2021.	Indication accounts for less than 10% of use
Magnolo N, et al. Secukinumab treatment demonstrated high efficacy and safety in pediatric patients with moderate to severe plaque psoriasis: 52-week results from a randomized trial. Ann Am Acad Dermatol 2021.	Low-quality evidence
Magnolo N, et al. A phase 3 open-label, randomized multicenter study to evaluate efficacy and safety of secukinumab in pediatric patients with moderate to severe plaque psoriasis: 24-week results. J Am Acad Dermatol 2021.	Low-quality evidence
Magnolo N, et al. Secukinumab is Highly Efficacious and Has a Favorable Safety Profile in Pediatric Patients With Moderate-to-Severe Plaque Psoriasis. Ann Am Acad Dermatol 2020.	Low-quality evidence
Soenen R, et al. Therapeutic drug monitoring in dermatology: the way towards dose optimization of secukinumab in chronic plaque psoriasis. Clin Exp Dermatol 2022.	Outcomes not relevant to our scope

Citation	Decision
Yiu ZZN, et al. Drug survival of adalimumab, ustekinumab and secukinumab in patients with psoriasis: a prospective cohort study from the British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR). Br J Dermatol 2020.	Outcomes not relevant to our scope
Poddubnyy D, et al. Rapid improvement in spinal pain in patients with axial spondyloarthritis treated with secukinumab: primary results from a randomized controlled phase-IIIb trial. Ther Adv Musculoskelet Dis 2021.	Previously known information about secukinumab related to efficacy
McInnes IB, et al. Secukinumab versus adalimumab for treatment of active psoriatic arthritis (EXCEED): a double-blind, parallel-group, randomised, active-controlled, phase 3b trial. Lancet 2020.	Previously known information about secukinumab related to efficacy
McInnes, I. Residual Disease Activity in Psoriatic Arthritis Patients Treated with Secukinumab and Adalimumab Who Achieved Remission or Low DiseaseActivity: Results from a Phase 3b, Randomized, Double-blinded, Active-controlled, Head-to-head Study. Arthritis Rheum 2020.	Previously known information about secukinumab related to efficacy
Gottlieb AB, et al. Efficacy of secukinumab and adalimumab in patients with psoriatic arthritis and concomitant moderate-to-severe plaque psoriasis: results from EXCEED, a randomized, double-blind head-to-head monotherapy study. Br J Dermatol 2021.	Previously known information about secukinumab related to efficacy
van der Heijde D, et al. Secukinumab provides sustained low rates of radiographic progression in psoriatic arthritis: 52-week results from a phase 3 study, FUTURE 5. Rheumatology 2020.	Previously known information about secukinumab related to efficacy
Strand V, et al. The effect of secukinumab on patient-reported outcomes in patients with active psoriatic arthritis in a randomised phase 3 trial. Lancet 2022.	Previously known information about secukinumab related to efficacy
D'agostino MA, et al. Response to secukinumab on synovitis using Power Doppler ultrasound in psoriatic arthritis: 12-week results from a phase III study, ULTIMATE. Rheumatology (Oxford) 2022.	Previously known information about secukinumab related to efficacy
Reich K, et al. Secukinumab 2-weekly vs. 4-weekly dosing in patients with plaque-type psoriasis: results from the randomized GAIN study. Br J Dermatol 2021.	Previously known information about secukinumab related to efficacy
Reich K, et al. Secukinumab dosing optimization in patients with moderate-to-severe plaque psoriasis: results from the randomized, open-label OPTIMISE study. Br J Dermatol 2020.	Previously known information about secukinumab related to efficacy
Augustin M, et al. Secukinumab dosing every two weeks demonstrated superior efficacy compared to dosing every four weeks in psoriasis patients weighing 90 kg or more. J Eur Acad Dermatol Venereol 2020.	Previously known information about secukinumab related to efficacy
Bagel J, et al. Secukinumab maintains superiority over ustekinumab in clearing skin and improving quality of life in patients with moderate to severe plaque psoriasis: 52-week results from a double-blind phase 3b trial (CLARITY). J Eur Acad Dermatol Venereol 2021.	Previously known information about secukinumab related to efficacy
Orbai AM, et al. Secukinumab Efficacy on Psoriatic Arthritis GRAPPA-OMERACT Core Domains in Patients with or Without Prior Tumor Necrosis Factor Inhibitor Use: Pooled Analysis of Four Phase 3 Studies. Rheumatol Ther 2021.	Previously known information about secukinumab related to efficacy
Orbai AM, et al. Effect of Secukinumab on the Different GRAPPA-OMERACT Core Domains in Psoriatic Arthritis: A Pooled Analysis of 2049 Patients. J Rheumatol 2020.	Previously known information about secukinumab related to efficacy
Schett G, et al. Secukinumab Efficacy on Enthesitis in Patients With Ankylosing Spondylitis: Pooled Analysis of Four Pivotal Phase III Studies. J Rheumatol 2020.	Previously known information about secukinumab related to efficacy

Citation	Decision
Kirkham B, et al. Secukinumab in the Treatment of Dactylitis in Patients with Psoriatic Arthritis: Post Hoc Analysis Results from a Randomized Phase 3 Trial. Arthritis Rheumatol 2020.	Previously known information about secukinumab related to efficacy
Armstrong AW, et al. Patient Satisfaction With Secukinumab on Clearing the Skin of Patients With Plaque Psoriasis: Results From US Dermatology Electronic Medical Records. Maui Derm 2021.	Previously known information about secukinumab related to efficacy
Armstrong AW, et al. Secukinumab Improves Real-World Effectiveness Outcomes in Patients With Psoriasis Through 18 Months of Follow-Up: Analysis of US Dermatology Electronic Medical Records. Innov Dermatol Virtual Spring Conference 2021.	Previously known information about secukinumab related to efficacy
Armstrong AW, et al. Patient Satisfaction With Secukinumab on Clearing the Skin of Psoriasis: Results From US Dermatology Electronic Medical Records. Am Acad Dermatol Virtual Meeting Experience 2021.	Previously known information about secukinumab related to efficacy
Dauden E, et al. Long-term safety of nine systemic medications for psoriasis: A cohort study using the Spanish Registry of Adverse Events for Biological Therapy in Dermatological Diseases (BIOBADADERM) Registry. J Am Acad Dermatol 2020.	Previously known information about secukinumab related to efficacy
Moreno-Ramos MJ, et al. Real-World Effectiveness and Treatment Retention of Secukinumab in Patients with Psoriatic Arthritis and Axial Spondyloarthritis: A Descriptive Observational Analysis of the Spanish BIOBADASER Registry. Rheumatol Ther 2022.	Previously known information about secukinumab related to efficacy
Augustin M, et al. Real-world evidence of secukinumab in psoriasis treatment – a meta-analysis of 43 studies. J eur Acac Dermatol Venereol 2020.	Previously known information about secukinumab related to efficacy
Huang F, et al. Secukinumab provided significant and sustained improvement in the signs and symptoms of ankylosing spondylitis: results from the 52-week, Phase III China-centric study, MEASURE 5. Chin Med J 2020.	Previously known information about secukinumab related to safety
Elewski BE, et al. Association of Secukinumab Treatment With Tuberculosis Reactivation in Patients With Psoriasis, Psoriatic Arthritis, or Ankylosing Spondylitis. JAMA Dermatol 2021.	Previously known information about secukinumab related to safety
Lebwohl M, et al. The risk of malignancy in patients with secukinumab-treated psoriasis, psoriatic arthritis and ankylosing spondylitis: analysis of clinical trial and postmarketing surveillance data with up to five years of follow-up. Br J Dermatol 2021.	Previously known information about secukinumab related to safety
Agafonova E, et al. The Efficiency of Treatment of Coxitis in Axial Spondyloarthritis: Experience of Real Clinical Practice. Ann Rheumatol 2021.	Previously known information about secukinumab related to safety
Kiltz U, et al. Impact of Intermediate Treatment Interruption on Secukinumab Efficacy in Patients with Active Psoriatic Arthritis and Ankylosing Spondylitis: Interim Analysis Results from the SERENA Study. Arthititis Rheumatol 2021.	Previously known information about secukinumab related to safety
Nguyen T, et al. Secukinumab in US Biologic-Naive Patients With Psoriatic Arthritis: Results From the Randomized, Placebo-Controlled CHOICE Study. J Rheumatol 2022.	Study outside timeframe of our review
Augustin M, et al. Secukinumab dosing every 2 weeks demonstrated superior efficacy compared with dosing every 4 weeks in patients with psoriasis weighing 90 kg or more: results of a randomized controlled trial. Br J Dermatol 2022.	Study outside timeframe of our review
Kiltz U, et al. Long-term retention, effectiveness and safety of secukinumab in patients with active psoriatic arthritis or ankylosing spondylitis: Results from	Study outside timeframe of our review

Citation	Decision
the observational SERENA study. Ann Eur Congress Rheumatol Hybrid Congress 2022.	
Mease PJ, et al. Effectiveness of 6-month Use of Secukinumab in Patients With Psoriatic Arthritis in the CorEvitas Psoriatic Arthritis/Spondyloarthritis Registry. J Rheumatol 2022.	Study outside timeframe of our review
Strober B, et al. Utilization Trends and Impact of Secukinumab Treatment on Clinical Outcomes in Biologic-Naive Patients with Psoriasis in a US Real-World Setting. Dermatol Ther (Heidelb) 2022.	Study outside timeframe of our review

Appendix B. Xifaxan®

Appendix Table B1. References Submitted by Bausch

Citation	Decision
N/A	N/A

Appendix C. Invega Sustenna®/Trinza®

Appendix Table C1. References Submitted by Janssen

Citation	Decision
N/A	N/A

Appendix D. Tremfya®

Appendix Table D1. References Identified by ICER Systematic Literature Review

Citation	Decision
McGonagle, Dennis, et al. Resolution of enthesitis by guselkumab and relationships to disease burden: 1-year results of two phase 3 psoriatic arthritis studies. Rheumatology 2021;60:5337-5350	Previously known information about Tremfya related to efficacy

Appendix E. Prolia®

Appendix Table E1. References Submitted by Amgen

Citation	Decision
Hans D, McDermott M, Huang S, Kim M, Shevroja E, Mcclung M. Long-term Effect of Denosumab on Bone Microarchitecture as Assessed by Tissue Thickness – Adjusted Trabecular Bone Score in Postmenopausal Women with osteoporosis: Results from the FREEDOM and Open-label Extension. Poster Presented at The International Society for Clinical Densitometry (ISCD)'s 28th Annual Meeting. 2022 Mar.	Study published outside the timeframe of our review
Kim M. Comparing the effectiveness of osteoporosis therapies for fracture risk reduction using real-world data. Presented at: WCO-IOF ESCEO; 2022 Mar.	Study published outside the timeframe of our review
Spangler L, Nielson C, Brookhart MA, Hernandez RK, Stad RK, Lin T. Myocardial infarction and stroke risks among patients who initiated treatment with denosumab or zoledronic acid for osteoporosis	Study published outside the timeframe of our review

Appendix F. Entyvio®

Appendix Table F1. References Submitted by Takeda

Citation	Decision
Bohm M, et al. Comparative safety and effectiveness of vedolizumab to tumour necrosis factor antagonist therapy for Crohn's disease. Aliment Pharmacol Ther. 2020;52(4):669-681	(New) evidence of no clinical improvement with vedolizumab
Travis S, et al. P0448. Efficacy and safety of intravenous vedolizumab for treatment of chronic pouchitis: results of the phase 4 EARNEST trial. United European Gastroenterol J. 2021; (suppl 8):531.	Indication accounts for less than 10% of use
Schwartz DA, et al. Efficacy and safety of 2 vedolizumab intravenous regimens for perianal fistulizing Crohn's disease: ENTERPRISE study [published online ahead of print September 29, 2021]. Clin Gastroenterol Hepatol.	Intervention/comparison not relevant to scope
Ortendahl J, et al. P0572. Costs for treating patients with ulcerative colitis with vedolizumab or adalimumab based on endoscopic improvement data from the VARSITY trial. Presented at the ACG 2021 Annual Scientific Meeting. 22-27 October 2021, Las Vegas, Nevada.	Outcomes not relevant to our scope
Ghosh T, et al. P472. Payer-addressable burden of Crohn's disease in patients treated with ustekinumab and vedolizumab in the United States. Presented at the 16th Congress of European Crohn's and Colitis Organisation. July 2-3 & 8-10, 2021 (virtual).	Outcomes not relevant to our scope
Kuharic M, et al. P042. Early versus later use of vedolizumab in IBD: patient characteristics and treatment patterns in the real world (RALEE). Presented at AIBD 2021 Annual Meeting. December 9-11, 2021; Orlando, FL and virtual.	Outcomes not relevant to our scope
Danese S, et al. Vedolizumab treatment persistence and safety in a 2 year data analysis of an extended access programme. Aliment Pharmacol Ther. 2021;53(2):265-272.	Outcomes not relevant to our scope
Peyrin-Biroulet L, et al. Histologic outcomes with vedolizumab vs adalimumab in ulcerative colitis: results from an efficacy and safety study of vedolizumab intravenous compared to adalimumab subcutaneous in participants with ulcerative colitis (VARSITY). Gastroenterology. 2021;161(4):1156-1167.	Previously known information about vedolizumab related to efficacy
Sandborn WJ, et al. Efficacy and safety of vedolizumab subcutaneous formulation in a randomized trial of patients with ulcerative colitis. Gastroenterology. 2020;158(3):562-572.	Previously known information about vedolizumab related to efficacy
D'Haens et al. P366. Vedolizumab maintenance therapy reduced use of corticosteroids in patients with Crohn's disease in the GEMINI 2 trial. J Crohns Colitis. 2021;15(suppl 1):S383-S385.	Previously known information about vedolizumab related to efficacy
Dubinsky M et al. Sa083. Symptomatic improvement with vedolizumab therapy for Crohn's disease stratified by disease activity and prior tumor necrosis factor antagonist failure: post hoc analyses from the GEMINI 2 trial. Gastroenterology. 2021;160(6):S-414.	Previously known information about vedolizumab related to efficacy
Dulai PS, et al. Early intervention with vedolizumab on longer term surgery rates in Crohn's disease: post hoc analysis of the GEMINI phase 3 and long-term safety programs. J Crohns Colitis. 2021;15(2):195-202.	Previously known information about vedolizumab related to efficacy

Citation	Decision
Cleveland NK, et al. P2649. Persistence of first and second lines of biologic treatment across different treatment sequences in patients with inflammatory bowel disease receiving at least two biologics: findings from ROTARY Part A. Presented at the ACG 2021 Annual Scientific Meeting. October 22-27 2021, Las Vegas, Nevada	Previously known information about vedolizumab related to efficacy
Danese S, et al. Su463. Vedolizumab rates of mucosal healing in Crohn's disease: a systematic literature review and meta-analysis of real-world data. Presented at the 2021 Digestive Disease Week Virtual Conference. May 23, 2021 (virtual).	Previously known information about vedolizumab related to efficacy
Bressler B, et al. Vedolizumab and anti-tumour necrosis factor α real-world outcomes in biologic naïve inflammatory bowel disease patients: results from the EVOLVE Study. J Crohns Colitis. 2021;15(10):1694-1706.	Previously known information about vedolizumab related to efficacy
Schultz BG, Diakite I, Carter JA, Snedecor SJ, Turpin R. Cost-effectiveness of intravenous vedolizumab vs subcutaneous adalimumab for moderately to severely active ulcerative colitis. J Manag Care Spec Pharm. 2021 Nov;27(11):1592-1600.	Previously known information about vedolizumab related to efficacy
Loftus EV, et al. Sustained corticosteroid-free clinical remission during vedolizumab maintenance therapy in patients with ulcerative colitis on stable concomitant corticosteroids during induction therapy: a post hoc analysis of GEMINI 1. Clin Exp Gastroenterol. 2020c;13:211-220.	Previously known information about vedolizumab related to efficacy
Kochar B, et al. Vedolizumab is associated with a lower risk of serious infections than anti-tumor necrosis factor agents in older adults [published online ahead of print September 3, 2021]. Clin Gastroenterol Hepatol.	Previously known information about vedolizumab related to safety
Loftus EV, Jr, Feagan BG, Panaccione R, et al. Long-term safety of vedolizumab for inflammatory bowel disease. Aliment Pharmacol Ther. 2020;52(8):1353-1365.	Previously known information about vedolizumab related to safety
Singh S, et al. Risk of malignancy with vedolizumab vs tumor necrosis factor-α antagonists in patients with inflammatory bowel diseases [published online ahead of print June 3, 2021]. Dig Dis Sci.	Previously known information about vedolizumab related to safety
Khan N, et al. Incidence of infections and malignancy among elderly male patients with IBD exposed to vedolizumab, prednisone, and 5-ASA medications: a nationwide retrospective cohort study. Adv Ther. 2021;38(5):2586-2598.	Previously known information about vedolizumab related to safety
Sands BE, et al. Vedolizumab versus adalimumab for moderate-to-severe ulcerative colitis. N Engl J Med. 2019;381:1215-1226.	Study published outside of the timeframe of our review

Appendix G. Promacta®

Appendix Table G1. References Submitted by Novartis

Citation	Decision
N/A	N/A

Appendix H. Jakafi®

Appendix Table H1. References Submitted by Incyte

Citation	Decision
VersIovsek S et al. Real— world survival of US patients with intermediate- to high-risk mgelof ibrosis: impact of ruxolitinib approval. Ann Hematol 2022; 101:131-137. (Epub online ahead of print October 9, 2021)	Low-quality evidence
VersIovsek S et al. Changes in the incidence and overall survival of patients with myeloproliferative neoplasms between 2002 and 2016 in the United States. Leuk Lymphoma 2022; 63:694—702. (Epub online ahead of print October 25, 2021)	Low-quality evidence
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
Kiladjian et al. Long-term efficacy and safety of ruxolitinib versus best available therapy in polycythaemia vera (RESPONSE): 5—year follow up of a phase 3 study. Lancet Haematol 2020; 7:e226-e237.	Previously known information about ruxolitinib related to efficacy
Passamonti F, Palandr i F, Saddam G, et al. Long- term effect of ruxolitinib (RUX) in inadequately controlled polgcgthemia ver a (PV) without splenomegalg: 5-gear results from the Phase 3 RESPONSE—2 study [virtual presentation]. Presented at: 62nd Annual Meeting of the American Society of Hematology; December 5—8, 2020	Previously known information about ruxolitinib related to efficacy
Al-Ali HK et al. Primary analysis of JUMP, a phase 3b, expanded-access study evaluating the safety and efficacy of ruxolitinib in patients with myelofibrosis, including those with low platelet counts. Br J Haematol 2020; 189:888-903	Previously known information about ruxolitinib related to efficacy

Appendix I. Rexulti®

Appendix Table I1. References Submitted by Otsuka

Citation	Decision
Dragheim M et al. Safety and tolerability of flexible-dose brexpiprazole as maintenance treatment in adolescents with schizophrenia: A long-term, multicenter, open-label study. Psych Congress 2021; October 29 – November 1, 2021; San Antonio TX, US	Indication accounts for less than 10% of use
McIntyre R, et al. The influence of baseline functioning on life engagement outcomes: post hoc analysis of three brexpiprazole studies in major depressive disorder. European Neuropsychopharmacology,2021;53(suppl. 1) S509.	Duplicate information
Meehan RJ, et al. Adjunctive brexpiprazole in patients with MDD and anxiety symptoms: Results from posthoc analyses of three placebo-controlled studies. Australian and New Zealand Journal of Psychiatry. 2021; 55.SUPPL 1: 112-113.	Duplicate information
Yan T, Greene M, Chang E, et al. Impact of atypical antipsychotics as adjunctive therapy on psychiatric cost and utilization in patients with major depressive disorder. Clinicoecon Outcomes Res. 2020;12:81-89. doi: 10.2147/CEOR.S231824.	Low-quality evidence
Yan T, Greene M, Chen E, et al. Health care costs in patients with schizophrenia treated with brexpiprazole versus other oral atypical antipsychotic therapy. Clin Ther. 2020;42(1):77-92.	Low-quality evidence
Weiss C, et al. Effects of adjunctive brexpiprazole on calmness and life engagement in major depressive disorder: post hoc analysis of patient-reported outcomes from clinical trial exit interviews. Journal of Patient-Reported Outcomes 2021;5.1: 128.	Low-quality evidence
McIntyre R, et al. The influence of baseline functioning on life engagement outcomes: post hoc analysis of three brexpiprazole studies in major depressive disorder. European Neuropsychopharmacology,2021;53(suppl. 1) S509.	Low-quality evidence
Krystal A, et al. Chronobiologic parameter changes in patients with major depressive disorder and sleep disturbance treated with adjunctive brexpiprazole: An open-label, flexible-dose, exploratory sub-study. J Affective Disorders. 2021;278:288-295	Low-quality evidence
Wee SN, et al. Patient life engagement improvements associated with brexpiprazole. Presented at Psych Congress 2021; October 29 – November 1, 2021; San Antonio TX, US	Previously known information about Rexulti related to efficacy
Seetasith A, Greene M, Hartry A, et al. Real-world economic outcomes of brexpiprazole and extended-release quetiapine adjunctive use in major depressive disorder. ClinicoEconomics and Outcomes Research. 2019;11:741	Study published outside of the timeframe of our review
Broder MS, Greene M, Yan T, et al. Medication adherence, health care utilization, and costs in patients with major depressive disorder initiating adjunctive atypical antipsychotic treatment. Clin Ther. 2019;41(2):221-32.	Study published outside of the timeframe of our review
Correll CU, He Y, Therrien F, et al. Effects of brexpiprazole on functioning in patients with schizophrenia: post hoc analysis of short- and long-term studies. J Clin Psych. 2022;8(2):20m13793.	Study published outside of the timeframe of our review
Molina S, et al. Economic evaluation of brexpiprazole as adjunctive treatment of major depressive disorder in the Mexican National Health System. Presented at International Society of Pharmacoeocnomics and Outcomes Research Annual Meeting 2022, May 15–18, 2022; Washington, DC, USA	Study published outside of the timeframe of our review

Citation	Decision
Bruno CD, et al. Impact of obesity on brexpiprazole pharmacokinetics: proposal for improved initiation of treatment. J Clinical Pharmacology; 2022;62(1)	Study published outside of the timeframe of our review
Thase M, et al. Adjunctive brexpiprazole in patients with major depressive disorder and anxiety symptoms: Post hoc analyses of three placebo-controlled studies. Neuropsychiatric Disease and Treatment 2019;15: 37-45.	Study published outside of the timeframe of our review

Appendix J. Lupron®

Appendix Table J1. References Submitted by AbbVie

Citation	Decision
Wallach JD, Deng Y, McCoy RG, et al. Real-world Cardiovascular Outcomes Associated With Degarelix vs Leuprolide for Prostate Cancer Treatment. JAMA Netw Open. 2021; 4(10): e2130587	Low-quality evidence
Vargas Trujillo M, Dragnic S, Aldridge P, Klein KO. Importance of individualizing treatment decisions in girls with central precocious puberty when initiating treatment after age 7 years or continuing beyond a chronological age of 10 years or a bone age of 12 years. J Pediatr Endocrinol Metab. 2021 Apr 15;34(6):733-739. doi: 10.1515/jpem-2021-0114. PMID: 33856747.	Low-quality evidence

Appendix K. Somatuline® Depot

Appendix Table K1. References Submitted by Ipsen

Citation	Decision
Faggiano A, Modica R, Lo Calzo F, et al. Lanreotide Therapy vs Active Surveillance in MEN1-Related Pancreatic Neuroendocrine Tumors < 2 Centimeters. The Journal of Clinical Endocrinology & Metabolism 2020. 105: 78–84.	Low-quality evidence
Mendis S, Jao J, Lee MKC, et al. Real-World Comparison of Lanreotide and Octreotide LAR Use for Neuroendocrine Tumours (NETs) in British Columbia, Canada. North American Neuroendocrine Tumor Society 2019. C–2: 55–56.	Low-quality evidence
Cheung WY, Feuilly M, Laforty C, et al. A real-world observational study of somatostatin analogue use and costs in Canada. JCO 2020. 38: 608–608.	Low-quality evidence
Loree J, Feuilly M, Laforty C, *et al.* Real-World Comparative Analysis Of Lanreotide Autogel And Octreotide LAR Use For Neuroendocrine Tumors (NETs) In Canada. *The North American Neuroendocrine Tumor Society (NANETS)* 2019. Poster presented at the NANETS Annual Multidisciplinary NET Disease Symposium:	Low-quality evidence
Prasad V, Srirajaskanthan R, Toumpanakis C, et al. Lessons from a multicentre retrospective study of peptide receptor radionuclide therapy combined with lanreotide for neuroendocrine tumours: a need for standardised practice. Eur J Nucl Med Mol Imaging 2020. 47: 2358–2371.	Low-quality evidence
Ryan P, McBride A, Ray D, et al. Lanreotide vs octreotide LAR for patients with advanced gastroenteropancreatic neuroendocrine tumors: An observational time and motion analysis. J Oncol Pharm Pract 2019. 25: 1425–1433.	Outcomes not relevant to our scope
Ström T, Kozlovacki G, Myrenfors P, et al. Patient And Nurse Experience Of Using Somatostatin Analogues To Treat Gastroenteropancreatic Neuroendocrine Tumors: Results Of The Somatostatin Treatment Experience Trial (STREET). PPA 2019. Volume 13: 1799–1807.	Outcomes not relevant to our scope
Walter T, Eskenazi M, Rama N, et al. Patient and nurse satisfaction with the new lanreotide autogel pre-filled syringe in neuroendocrine tumors (NET): a prospective study (SONATE). European Neuroendocrine Tumor Society (ENETS) at <https://www.enets.org/abstract/patient-and-nurse-satisfaction-with-the-new-lanreotide-autogel-pre-filled-syringe-in-neuroendocrine-tumors-net-a-prospective-study-sonate.html>	Outcomes not relevant to our scope
Klink AJ, Feinberg B, Yu H-T, et al. Patterns of Care Among Real-World Patients with Metastatic Neuroendocrine Tumors. The Oncologist 2019. 24: 1331–1339.	Outcomes not relevant to our scope
Lepage C, Phelip JM, Lièvre A, *et al.* 1163P Lanreotide as maintenance therapy after first-line treatment in patients with non-resectable duodeno-pancreatic neuroendocrine tumours (NETs): An international double-blind, placebo-controlled randomized phase II trial. *Annals of Oncology* 2020. 31: S774	Study population outside approved label indication
Paulson S, Ray D, Aranha S, *et al.* Lanreotide Depot to Treat Gastroenteropancreatic Neuroendocrine Tumors in a US Community Oncology Setting: A Prospective, Observational Study [Manuscript in development].	Study published outside of the timeframe of our review
Pusceddu S, Vernieri C, Di Maio M, et al. Impact of Diabetes and Metformin Use on Enteropancreatic Neuroendocrine Tumors: Post Hoc Analysis of the CLARINET Study. Cancers (Basel) 2021. 14: 69	Study published outside of the timeframe of our review

Citation	Decision
Paul A, Mendis S, Jao J, et al. Comparison of Lanreotide and Octreotide LAR use and outcomes for gastrointestinal neuroendocrine tumors in British Columbia, Canada. in BC Cancer (2022).	Study published outside of the timeframe of our review
Adelman D, Burgess A, & Davies. Evaluation of long-acting somatostatin analog injection devices by nurses: a quantitative study. MDER 2012. 103. doi:10.2147/MDER.S37831	Study published outside of the timeframe of our review
Pavel M, Ćwikła JB, Lombard-Bohas C, et al. Efficacy and safety of high-dose lanreotide autogel in patients with progressive pancreatic or midgut neuroendocrine tumours: CLARINET FORTE phase 2 study results. European Journal of Cancer 2021. 157: 403–414.	Study published outside of the timeframe of our review
Baudin E, Horsch D, Singh S, et al. Lanreotide autogel/depot in patients with advanced bronchopulmonary neuroendocrine tumors: results from the phase 3 SPINET study. Presented at European Society for Medical Oncology Congress; 2021 Sep 16-21; Virtual	Study published outside of the timeframe of our review

Appendix L. Adcetris®

Appendix Table L1. References Submitted by Seagan

Citation	Decision
Steiner R BM, et al,: ADCETRIS with Chemotherapy in Frontline Treatment of Classic Hodgkin Lymphoma Nodular Sclerosis Syncytial Variant. Blood 136, 2020	Indication accounts for less than 10% of use
Dummer R, Prince HM, Whittaker S, et al: Patient-reported quality of life in patients with relapsed/refractory cutaneous T-cell lymphoma: Results from the randomised phase III ALCANZA study. Eur J Cancer 133:120-130, 2020	Low-quality evidence
Kaloyannidis P, Hertzberg M, Webb K, et al: ADCETRIS for the treatment of patients with relapsed or refractory Hodgkin lymphoma after autologous stem cell transplantation. Br J Haematol 188:540-549, 2020	Low-quality evidence
Pinczes LI, Szabo R, Illes A, et al: Real-world efficacy of ADCETRIS plus bendamustine as a bridge to autologous hematopoietic stem cell transplantation in primary refractory or relapsed classical Hodgkin lymphoma. Ann Hematol 99:2385-2392, 2020	Low-quality evidence
Iannitto E, Romano A, Scalzulli PR, et al: ADCETRIS in association with bendamustine in refractory or multiple relapsed Hodgkin lymphoma. A retrospective real-world study. European Journal of Haematology 104:581-587, 2020	Low-quality evidence
Ionova T, Afanasyev B, Andrievskih M, et al: Objective response rates and quality of life changes in patients with relapsed/refractory Hodgkin lymphoma (RR HL) receiving ADCETRIS as > 2 line of treatment in the real world setting. HemaSphere 4:527-528, 2020	Low-quality evidence
Wagner SM, Melchardt T, Egle A, et al: Treatment with ADCETRIS plus bendamustine in unselected patients with CD30-positive aggressive lymphomas. European Journal of Haematology 104:251-258, 2020	Low-quality evidence
Horwitz S, O'Connor OA, Pro B, et al: ADCETRIS with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. Lancet 393:229-240, 2019	Previously known information about brentuximab vedotin related to efficacy
Horwitz S OCO, Pro B, Illidge T, Swaminathan I, et al,: The ECHELON-2 Trial: 5-Year Results of a Randomized, Double-Blind, Phase 3 Study of ADCETRIS and CHP (ADCETRIS+CHP) Versus CHOP in Frontline Treatment of Patients with CD30-positive Peripheral T-Cell Lymphoma. American Society of Hematology Annual Meeting; Virtual; December 5-8, Abstract No. 1150, 2020	Previously known information about brentuximab vedotin related to efficacy
Straus DJ, Dlugosz-Danecka M, Alekseev S, et al: ADCETRIS with chemotherapy for stage III/IV classical Hodgkin lymphoma: 3-year update of the ECHELON-1 study. Blood 135:735-742, 2020	Previously known information about brentuximab vedotin related to efficacy
Straus DJ D-DM, Connors JM, et al,: ADCETRIS with Chemotherapy for Patients with Previously Untreated, Stage III/IV Classical Hodgkin Lymphoma: 5-Year Update of the ECHELON-1 Study. Electronic poster presentation at the virtual 62nd Annual Meeting of the American Society of Hematology (ASH), December 5–8, 2020, Abstract No. 2973, 2020	Previously known information about brentuximab vedotin related to efficacy
Steiner R, Cramer FM, Singh P, et al: ADCETRIS with chemotherapy for advanced stage untreated classic Hodgkin's lymphoma in a real-world setting. Journal of Clinical Oncology 38, 2020	Previously known information about brentuximab vedotin related to efficacy

Citation	Decision
Ferhanoglu B, Altuntas F, Ozbalak M, et al: ADCETRIS consolidation therapy after autologous stem-cell transplantation in patients with high-risk Hodgkin's lymphoma: Multicenter real-life experience. HemaSphere 4:534-535, 2020	Previously known information about brentuximab vedotin related to efficacy
Chavda N, Robinson S, Boumendil A, et al: ADCETRIS for relapse after autologous stem cell transplant in patients with hodgkin lymphoma. A study of the LWP-EBMT. Bone Marrow Transplantation 55:116-117, 2020	Previously known information about brentuximab vedotin related to efficacy
Gillatt M, Markarian A, Nakashima L, et al: Use, response, and outcomes of ADCETRIS in transplant-ineligible patients for relapsed/refractory hodgkin lymphoma. Journal of Oncology Pharmacy Practice 26:14, 2020	Previously known information about brentuximab vedotin related to efficacy
Özbalak M, Salihoğlu A, Soysal T, et al: Long-term results of ADCETRIS in relapsed and refractory Hodgkin lymphoma: multi-center real-life experience. Annals of Hematology 99:301-307, 2020	Previously known information about brentuximab vedotin related to efficacy
von Tresckow B, Bergamasco A, Trinchese F, et al: Effectiveness of ADCETRIS in relapsed/refractory classic Hodgkin lymphoma: A systematic review and meta-analysis. Annals of Oncology 31:S650, 2020	Previously known information about brentuximab vedotin related to efficacy
Horwitz S, O'Connor OA, Pro B, et al: The ECHELON-2 Trial: 5-year results of a randomized, phase III study of ADCETRIS with chemotherapy for CD30-positive peripheral T-cell lymphoma. Ann Oncol 33:288-298, 2022	Study published outside of the timeframe of our review
Straus DJ, Dlugosz-Danecka M, Connors JM, et al: ADCETRIS with chemotherapy for stage III or IV classical Hodgkin lymphoma (ECHELON-1): 5-year update of an international, open-label, randomised, phase 3 trial. Lancet Haematol 8:e410-e421, 2021	Study published outside of the timeframe of our review
Ansell SM et al: First-line ADCETRIS plus chemotherapy to improve overall survival in patients with stage III/IV classical Hodgkin lymphoma: An updated analysis of ECHELON-1. Presented at ASCO 2022. Abstract 7503., 2022	Study published outside of the timeframe of our review
Horwitz SM, Scarisbrick JJ, Dummer R, et al: Randomized phase 3 ALCANZA study of ADCETRIS vs physician's choice in cutaneous T-cell lymphoma: final data. Blood Adv 5:5098-5106, 2021	Study published outside of the timeframe of our review

Appendix M. Krystexxa®

Appendix Table M1. References Submitted by Horizon Therapeutics

Citation	Decision
Abdellatif AA, et al. Pegloticase for uncontrolled gout in kidney transplant recipients: Early data report of a multicenter, open-label efficacy and safety study. Am Society Nephrol 2020 [abstract].	Indication accounts for less than 10% of use
Abdellatif AA, et al. Pegloticase for uncontrolled gout in kidney transplant recipients: Early data report of a multicenter, open-label efficacy and safety study. Am Society Nephrol 2020 [poster].	Indication accounts for less than 10% of use
Khanna P, et al. Reducing Immunogenicity of Pegloticase (RECIPE) with Concomitant Use of Mycophenolate Mofetil in Patients with Refractory Gout-a Phase II Double Blind Randomized Controlled Trial. Am College Rheumatol Meeting 2020 [abstract].	Intervention/comparison not relevant to scope
Khanna P, et al. Reducing Immunogenicity of Pegloticase (RECIPE) with Concomitant Use of Mycophenolate Mofetil in Patients with Refractory Gout-a Phase II Double Blind Randomized Controlled Trial. Am College Rheumatol Meeting 2020 [presentation].	Intervention/comparison not relevant to scope
Botson J, et al. A multicenter, efficacy and safety study of methotrexate to increase response rates in patients with uncontrolled gout receiving pegloticase (MIRROR): 12-month results of an open-label study. Am College Rheumatol 2020 [abstract].	Intervention/comparison not relevant to scope
Botson J, et al. A multicenter, efficacy and safety study of methotrexate to increase response rates in patients with uncontrolled gout receiving pegloticase (MIRROR): 12-month results of an open-label study. Am College Rheumatol 2020 [poster].	Intervention/comparison not relevant to scope
Botson JK, et al. Pretreatment and Coadministration With Methotrexate Improved Durability of Pegloticase Response: An Observational, Proof-of-Concept Case Series. J Clin Rheumatol 2020.	Intervention/comparison not relevant to scope
Albert JA, et al. Increased Efficacy and Tolerability of Pegloticase in Patients With Uncontrolled Gout Co-Treated With Methotrexate: A Retrospective Study. Rheumatol Ther 2020.	Intervention/comparison not relevant to scope
Baraf HS, et al. The Impact of Azathioprine on the Frequency of Persistent Responsiveness to Pegloticase in Patients with Chronic Refractory Gout. Am College Rheumatol 2020.	Intervention/comparison not relevant to scope
Rainey H, et al. Companion immunosuppression with azathioprine increases the frequency of persistent responsiveness to pegloticase in patients with chronic refractory gout. Am College Rheumatol 2020.	Intervention/comparison not relevant to scope
Masri KR, et al. Leflunomide co-therapy with pegloticase in uncontrolled gout. EULAR Eur Congress Rheumatol 2020 [abstract].	Intervention/comparison not relevant to scope
Masri K, et al. Leflunomide co-therapy with pegloticase in uncontrolled gout. Ann Rheumatol 2020 [poster].	Intervention/comparison not relevant to scope
Botson JK, et al. Pegloticase in combination with methotrexate in patients with uncontrolled gout: A multicenter, open-label study (MIRROR). J Rheumatol 2021.	Low-quality evidence
Johnson RL, et al. Pegloticase Treatment Significantly Decreases Blood Pressure in Patients with Chronic Gout. Hypertension 2019.	Low-quality evidence

Citation	Decision
Bleyer AJ, et al. A USRDS database study on the use of pegloticase in patients undergoing dialysis. Am Society Nephrol 2020 [abstract].	Low-quality evidence
Bleyer AJ, et al. A USRDS database study on the use of pegloticase in patients undergoing dialysis. Am Society Nephrol 2020 [poster].	Low-quality evidence
Song Y, et al. Pharmacokinetics of Pegloticase and Methotrexate Polyglutamate(s) in Patients with Uncontrolled Gout Receiving Pegloticase and Cotreatment of Methotrexate. Am College Rheumatol 2020 [abstract].	Outcomes not relevant to our scope
Song Y, et al. Pharmacokinetics of Pegloticase and Methotrexate Polyglutamate(s) in Patients with Uncontrolled Gout Receiving Pegloticase and Cotreatment of Methotrexate. Am College Rheumatol 2020 [poster].	Outcomes not relevant to our scope
LaMoreaux B, et al. Trends in Immunomodulation/pegloticase Co-therapy from 2015-2019: A Claims Database Study. Am College Rheumatol 2020 [abstract].	Outcomes not relevant to our scope
LaMoreaux B, et al. Trends in Immunomodulation/pegloticase Co-therapy from 2015-2019: A Claims Database Study. Am College Rheumatol 2020 [poster].	Outcomes not relevant to our scope
Soloman N, et al. Management of Gout with Pegloticase; Real-World Utilization and Outcomes from Trio Health and the American Rheumatology Network (ARN). Am College Rheumatol 2020 [abstract].	Outcomes not relevant to our scope
Soloman N, et al. Management of Gout with Pegloticase; Real-World Utilization and Outcomes from Trio Health and the American Rheumatology Network (ARN). Am College Rheumatol 2020 [poster].	Outcomes not relevant to our scope
Edwards NL, et al. Characterization of patients with chronic refractory gout who do and do not have clinically apparent tophi and their response to pegloticase. J Rheum 2019.	Outcomes not relevant to our scope
Schlesinger N, et al. Treatment with pegloticase improves hepatic fibrosis estimated by fibrosis-4 index in subjects with chronic refractory gout. EULAR Eur Congress Rheumatol 2020 [abstract].	Outcomes not relevant to our scope
Schlesinger N, et al. Treatment with pegloticase improves hepatic fibrosis estimated by fibrosis-4 index in subjects with chronic refractory gout. EULAR Eur Congress Rheumatol 2020 [poster].	Outcomes not relevant to our scope
Pillinger MH, et al. Dissociation between Clinical Benefit and Persistent Urate Lowering in Patients with Chronic Refractory Gout Treated with Pegloticase. J Rheumatol 2020.	Previously known information about pegloticase related to efficacy

Appendix N. ICER Systematic Literature Review

Appendix Table N1. ICER Systematic Literature Review Results

Drug	Search Yield	References Screened in Full-Text	New Evidence Identified
Lupron®	24	0	0
Entyvio®	14	0	0
Cosentyx®	22	4	1
Xifaxan®	18	1	0
Invega Sustenna®/ Invega Trinza®	8	0	0
Tremfya®	7	4	3
Prolia®	50	0	0
Promacta®	7	1	0
Jakafi®	25	1	1
Rexulti®	7	0	0
Somatuline® Depot	14	0	0
Adcetris®	5	0	0
Krystexxa®	3	0	0

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

Appendix Table N2. Sample Search Strategy in PubMed

((Lupron OR 'leuprolide acetate' OR leuprolidine OR 'leuprorelin acetate' OR A-43818 OR Abbott-43818 OR DC-2-269 OR TAP-144) AND (('Randomized controlled trial' OR 'randomised 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 2020/01/01:2021/12/31[dp])

Appendix O. 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 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 hazard ratio 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 hazard ratio is now calculated to be 0.75, there must have been a prior belief about what that hazard ratio 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 hazard ratio for survival would persist over time, and at eight years of follow-up the hazard ratio 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 hazard ratio 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
    a. ICER applies the same evidentiary standards to real-world evidence that it applies to all other forms of evidence and is happy to consider real-world evidence as part of the UPI report.
    b. High-quality real-world evidence 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, ICER only reviewed observational studies as part of the UPI report process 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 high-quality observational studies 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
	Bausch Health	
1.	We would like to note that the Abdel Moneim M et al. 2021 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 the difference in minimum inhibitory concentration of rifaximin of intervention v. control) was not significantly different amongst those in the rifaximin group (v. lactulose alone). However, they did report that those in the rifaximin group had significantly lower risk of developing HE and the time to the first episode of the 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. While the dose used in the study (i.e., 400 mg rifaximin 3 times daily) and the on-label study population does not conform to the FDA-approved Xifaxan label for HE, the study does show rifaximin's value in terms of a lower risk of the development of an HE episode and the time to an HE episode in line with the FDA label.	Please see GER 5a and 5b.
2.	Additionally, in your review the Patel VC et al. study was identified in your search, however, not screened as full text. This study found that amongst patients with cirrhosis and HE treated with rifaximin 550 mg, though the primary endpoint was not achieved (i.e. did not achieve 50% reduction in neutrophil oxidative burst at 30 days from baseline), at day 30 and 90 day from treatment initiation, the grade of HE normalized which is generally supportive of the "reduction in risk of breakthrough HE episode" seen in the pivotal trial for Xifaxan 550 mg (section 14 of FDA label). Failure to achieve the primary outcome in this study does not imply lack of efficacy, but rather points to a different mechanism by which rifaximin exerts its effects. The exclusion of critical evidence that supports Xifaxan's value further highlights our concerns with ICER's scientific rigor in identifying/critiquing this critical evidence.	Please see GER 1a, 1b, and 5a.
3.	What we want to highlight is ICER's assessment of the Jesudian AB, 2020 study during the 2020 and 2021 UPI cycle. Bausch had provided the Jesudian AB, 2020 (cost-effectiveness evidence) to support the value of XIFAXAN in HE for the 2020 and 2021 UPI. ICER deemed the study as "Study published outside of the timeframe of our review" for 2020 UPI and as "Previously known information about rifaximin related to cost" for 2021 UPI. We had disputed this characterization of this study in our 2021 Manufacturer Input Phase II response with details of why the study evidence supports and augments the value of XIFAXAN. In the final report posted by ICER on November 16, 2021, ICER stated: "We agree that Jesudian does potentially provide new information related to cost and we have reviewed it". However, you dismissed the study stating: "Economic models rarely provide high or moderate-quality evidence by GRADE criteria, and that matches with our conclusion about Jesudian." Further,	Thank you for your comments. However, we are not relitigating comments and submitted evidence from our prior report in this response to comments. If there are questions about decisions we made in prior reports, we are happy to have a phone call with representatives from the manufacturer's team to discuss the issues.

#	Comment	Response/Integration
	in your response you concluded that the Jesudian AB, 2020 did not provide high or moderate-quality evidence of a substantial benefit that was not previously known by stating: "As an example, the model in Jesudian assumes mortality benefits based on a single-arm, open-label study. Mortality is clearly central to the modelling and yet the evidence for effects on mortality is of low (or very low) quality." We disagree with your methodology in characterizing this evidence supporting Xifaxan's value. Before the Jesudian AB, 2020 study was sent to the Journal of Managed Care & Specialty Pharmacy for publication, we had conducted the following: 1. A targeted literature review to identify relevant articles that reported mortality among hospitalized and not hospitalized HE patients in the U.S.; 2. Critically evaluated quality (using RoB 2 tool, ROBINS-I checklist, and STROBE framework, as applicable , ,) of the relevant identified studies in step 1, and 3. Scenario analysis to: a. Evaluate the impact of assuming no mortality benefit associated with XIFAXAN; and b. Evaluate the impact of assuming mortality benefits from studies conducted/published after Jesudian AB, 2020. Hence, ICER's assumption and assessment of "Mortality is clearly central to the modelling and yet the evidence for effects on mortality is of low (or very low) quality" is a misinterpretation of the evidence submitted by Bausch. We would have gladly provided this information before November 2021 if ICER had asked for it. It is regrettable that ICER did not reach out to Bausch over the two years for this evidence and erroneously concluded that the Jesudian AB, 2020 is of poor quality. This is one of the reasons we are unsure if actively engaging in ICER's UPI process provides the most robust/transparent scientific interactions for our patients and payers.	
4.	The Volk ML, 2021 study submitted by Bausch during the UPI 2020 and 2021 cycles was deemed as "Study published outside of the timeframe of our review" by ICER. The Volk ML, 2021 study is the most recent and relevant U.S. real-world evidence available that highlights the reduction in healthcare utilization and costs associated with the use of and adherence to Xifaxan (v. lactulose alone) amongst patients with HE. The Volk ML, 2021 study findings have been central to payer interactions and have enabled several payers to make clinically appropriate decisions on Xifaxan coverage for patients with HE. Dismissing key pieces of recent and relevant evidence due to the restrictive evidence review period and search strategy trivializes the evidence supporting the value of Xifaxan. If you have a meaningful scientific critique of the Volk study, we would be glad to address it, but not engaging with Bausch and dismissing it in your final report would continue the same pattern as you	This reference was not submitted for the 2022 UPI report. Therefore, we will not be reviewing it as it is long past the deadline stated in the UPI protocol for evidence submission and evaluation of the 2022 UPI report.

#	Comment	Response/Integration
	have done with the Jesudian AB study, potentially diminishing the submitted evidence and its value for making informed decisions by key stakeholders.	
	Amgen	
1.	Use more accurate data sources: net price data sourced exclusively from SSR health has many limitations, particularly for physician-administered drugs like Prolia. ICER's use of SSR Health data incorrectly overestimates the net price change of Prolia. ICER's inclusion of Prolia in this report is based on pricing figures from SSR Health, a source inappropriate for ICER's net price calculations, which Amgen has previously brought to ICER's attention. SSR Health's use of averaged inputs compromise the reliability of price estimates. Furthermore, SSR Health is a far less accurate choice for physician-administered drugs like Prolia due to its limited capacity to record volume units and use of volume data from Symphony Health, which specializes in retail pricing data. Although ICER stated that Amgen did not offer alternative data, Amgen did in fact provide a more accurate net price calculation which was significantly lower than the estimate from SSR Health. This figure was derived from IQVIA, which boasts audit-level detail on 97% of non-retail U.S. drug sales. IQVIA is a trusted data source and the industry standard for critical business proceedings, making it a valid proxy for proprietary internal data. However, ICER rejected the lower, more accurate net price figure from IQVIA and persisted in citing SSR Health's steeply overestimated net price change.	ICER's protocol states that we estimate net price changes from SSR Health, but that we share such net price changes in confidence with manufacturers. The fact that Amgen states that the IQVIA data are more accurate than SSR Health in terms of Prolia's net price confirms that Amgen is aware of the true net price change for Prolia. ICER requested that Amgen (and other manufacturers) provide true estimate of change in net price. Had Amgen provided ICER with this information, it would have been used in place of the SSR Health data.
2.	Rate the results from the Singer et al. study as high-quality evidence as these results directly translate to patient-important outcomes. Patient-important outcomes are widely understood to include any variables that "reflect how a patient feels, functions, or survives." Persistence is a patient-important outcome: persisting with treatment leads to lower fracture rates resulting in patient avoidance of significant physical pain, preservation of independence, and prevention of stress from post-fracture care and rehabilitation. Improvement of patient-important outcomes is a key driving force in Amgen's research, and we believe evidence that is meaningful to patients is of the highest value. Amgen submitted four evidence sources that fulfill this criterion, yet ICER only accepted one and then discredited the outcomes of this study. Singer et al. demonstrate from claims data that Prolia users persisted longer with treatment than patients taking other anti-resorptive medicines, including oral bisphosphonates. In spite of the study's rigorous design and well-characterized sample population, ICER rated it as "low" quality evidence for having "uncertain" effects on patient-important outcomes. This directly contradicts a strong body of evidence connecting treatment persistence to patient-important outcomes; multiple studies show that persistent osteoporosis medication use correlates with greater reduction of fracture risk, significantly lower total healthcare costs, and reduced bone loss, all of which are immensely valuable to patients. This makes clear that the	We strongly disagree that persistence is a patient-important outcome. As an example, a placebo may have very high persistence if it is cheap, easy to take, and has no harms. Persistence is also affected by patient and provider beliefs about effectiveness. These beliefs do not constitute evidence.

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	higher persistence of Prolia in the Singer et al. study translates to greater overall benefits for patients. Rejecting this evidence for "indirectness" diminishes the patient experience and fails to account for its manifold and interconnected elements. It is crucial that payers and policymakers consider the patient journey more deeply before accepting vague dismissals of high-quality evidence. Value assessment works against its design when it results in policies that exacerbate undertreatment, which is a significant problem in osteoporosis. A recent global study showed that between 2005-2018, the number of hip fractures per 100,000 individuals in the U.S. was nearly double that of the U.K. and over five times the rate in Japan. This is concerning given that postmenopausal women experiencing a fracture have a 10% risk of another fracture within one year, contributing further to decline in function, diminished quality of life, and higher morbidity. , Additionally, while treatment rates within one year of fracture were down only 8% in the U.K. and up 11% in Japan (2013 to 2018), the U.S. saw a 31% decline, suggesting a disproportionate national shortfall in diagnosis and care. Without sufficient improvements in diagnosis and treatment, osteoporosis-related fracture care in the U.S. is projected to cost $95.2 billion annually by 2040. To reduce this immense economic burden and, more importantly, to relieve the degraded quality of life associated with osteoporosis, it is essential that non-restrictive coverage policies give patients a choice in their treatment options. Utilization management barriers also have broad implications on health equity and treatment gaps. Evidence suggests that non-Hispanic Black women have lower screening rates, higher rates of discharge without rehabilitative care, and 225% higher post-fracture destitution (i.e., becoming Medicaid dependent) than non-Hispanic white women. Improved access to osteoporosis diagnosis and treatment needs to be prioritized to close these gaps.	
3.	Incorporate direct drivers of the US healthcare system into the UPI report. Currently, ICER's methodology solely targets perceived budget impact and estimated net price change based on third party extrapolations. Public debate about the cost of medicines often focuses solely on the list price and does not account for the amount or quality of coverage, the rebates, or the discounts that are negotiated between a complex array of wholesalers, distributors, pharmaceutical benefits managers (PBMs), health plans, providers, and other entities. ICER's methodology does not recognize the complexity of the U.S. healthcare system (e.g., private and public state-specific systems with differing utilization patterns) or the influence of various third parties in payer contracts. In order to preserve patient access, negotiating formulary position is crucial, as both payers and PBMs impose high patient cost-sharing, establish utilization management	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.

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	barriers, or outright deny coverage if a drug is off-formulary or on a non-preferred formulary tier. ICER's UPI report does not measure impact on patient-important outcomes such as reduced fracture rates nor does it capture associated patient out-of-pocket cost-savings. ICER provides no discussion of the real-world value Prolia brings to patients and the health system. Given the complexity of real-world drug pricing, ICER's UPI methodology has many limitations. It is crucial that ICER takes a broader, all-encompassing approach that recognizes U.S. healthcare's complex underlying relationships and promotes coverage breadth and depth.	
	Takeda	
1.	Recommendation: Validate and contextualize price increases. Takeda is dedicated to improving patient health, and thus prices medicines in a way that makes them accessible to as many patients as possible, while recognizing the value they bring to patients, providers, and the overall healthcare system. In alignment with Takeda's pricing philosophy, over the last few years our annual gross and net price changes across our United States portfolio have been and continue to be single digit increases. ICER typically leverages net prices estimated from the SSR Health database, yet these are not validated, are often inaccurate, and consequently, may overestimate the real-world costs of drugs in IBD, including vedolizumab, paid by various plans. Takeda appreciates that ICER's draft report has cited the net price change that was shared with them, yet remains concerned with ICER's default use of the SSR Health database. Additionally, ICER notes that total market expenditure of vedolizumab increased over this time in order to highlight the impact of the price increase. However, total expenditure reflects both price and overall volume of use. Prescribing trends over the time period of the evaluation have demonstrated an increase in overall advanced biologic utilization, as well as an increase in use of vedolizumab compared to biologic medication options. We attribute this increase in uptake to revealed perception of value. This factor alone has an intuitive impact on overall expenditure, and it seems discrepant for ICER to interpret this with a negative lens rather than as an indication of value.	ICER's protocol states that we estimate net price changes from SSR Health, but that we share such net price changes in confidence with manufacturers. This is a fundamental step in ICER's validation process. The manufacturer provided corrections to the changes in net price and budget impact due to net price increases. These corrected values were used in the report. The budget impact measure that ICER focuses on within this report isolates impact derived from changes in the unit net price of vedolizumab within the US population. The utilization of vedolizumab is held fixed in this budget impact measure to not imply judgment related to either increases or decreases in volumes sold over time.
2.	Recommendation: Consider the full extent of clinical data. As part of the assessment, ICER aims to review new evidence for vedolizumab over the prior year. However, ICER continues to have opaque methodology, with subjective assessment of the magnitude of clinical effects demonstrated by new evidence, limited detail provided regarding why a study's outcomes are considered irrelevant, and exclusion of studies that add to a comprehensive body of evidence. For example, ICER explicitly rejects any evidence for indications composing less than 10% of the treated population, yet these smaller populations are important to consider in aggregate. There is high value to including studies with smaller subgroups in IBD, specifically, due	Please see GER 5a and 5b.

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	to the heterogeneous and chronic nature of the disease. The diversity of clinical presentation is so wide that looking at subgroups is how we share with providers information on where vedolizumab's effect is highly significant. As part of Takeda's emphasis on meeting an unmet need in IBD, there has been a continued commitment to generating scientific data and publishing high-quality, rigorous clinical trials and real-world data to identify the optimal use of vedolizumab for patients. Well over 100 clinical trials and observational studies of vedolizumab use in UC and/or CD have been published over the years including key studies such as the GEMINI trials, VARSITY trial, and VICTORY consortium, as well as the EARNEST and ENTERPRISE randomized-controlled trials (RCTs). Additionally, real-world studies such as EVOLVE, RALEE, and ROTARY, are among other ongoing studies that provide additional insight into the clinical effectiveness and safety of vedolizumab. Takeda previously provided a selection of references including recent RCTs and real world studies for ICER's consideration. Among these, ICER rejected information from the EARNEST trial (Travis et al 2021) as pertaining to a small population, yet this led to the European Commission expanding vedolizumab's approved indications – a demonstration of recognized value. Additionally, information that ICER deems "previously known regarding efficacy and safety" bolsters physician and patient understanding of who will benefit clinically from using vedolizumab, and thus enhances the picture of overall value. As noted above, prescribing trends have shown increased use of vedolizumab over the time period considered, thus indirectly indicating the perception of benefit within the healthcare system. Therefore, Takeda recommends that ICER consider all new published evidence, even those that impact smaller populations or reinforce understanding of benefit.	
	Incyte	
1.	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 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):	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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	○ 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).	
2.	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 REACH2 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. This evidence led to a new FDA-approved indication and multiple Category 1 upgrades 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 the data from RESPONSE, RESPONSE2 and JUMP demonstrate only "previously known information about ruxolitinib related to efficacy" and that the real-world evidence (RWE) studies constitute "low-quality evidence." These trials provided clinically meaningful long-term efficacy and safety data that help inform the benefit-risk profile of Jakafi. Further, our RWE studies have been recognized by the scientific community at global scientific congresses and in peer-reviewed hematology journals. Importantly, the studies described the impact of treatment with Jakafi on overall survival in MF in the post-approval setting and demonstrated the economic value of Jakafi in real-world clinical use.	Please see GER 1a, 1b, 3b, and 5a.
3.	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. During 2020-2021, Incyte invested more than $2.5 billion in research and development, which equated to nearly 50% of Incyte's total revenues during this period. This level of R&D investment is double that of the industry average of about 25% of revenues.	Incyte's investments in research and development are helpful context in concert with the price increase data presented within this report on Jakafi.
4.	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. The price of Jakafi is in the lower third of oral oncology monthly cost of therapy, and insurance companies support the use of Jakafi with ≥97% of covered lives with access to Jakafi.	Incyte's pricing policies are helpful context in concert with the price increase data presented within this report on Jakafi.
	Otsuka	

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1.	New clinical evidence has recently supported an important expanded indication demonstrating the clinical benefit of REXULTI for patients aged 13-17 with schizophrenia. While ICER claims that there is limited and low-quality new evidence to support changes in REXULTI's price, FDA granted a new indication for REXULTI in December 2021 based on the evidence submitted to ICER. Dragheim at al. (2021) reported that adolescent patients with schizophrenia showed sustained improvement in the Positive and Negative Symptom Scale (PANSS) Total score from baseline to Month 12 and to last visit during treatment with REXULTI. The mean change in PANSS Total score from baseline to last visit was -14.8 (80.5 vs. 65.7).1 This change in PANSS Total score in adolescents was similar to that seen in adults. The analysis by Kalaria et al. (2020) further provided the basis for extrapolating the efficacy of secongeneration antipsychotics from adults to adolescents. It quantitatively justified the similarity in placebo response and exposure–response between adults and adolescents in the treatment of schizophrenia. In Wang et al., an Otsuka-led analysis using aripiprazole adult and adolescent data further confirmed the key features of the efficacy extrapolation in Kalaria et al. and extended the analysis to REXULTI. The model predicted efficacy in adolescents. This provided additional support for the extrapolation of REXULTI's efficacy from adults to adolescents. These results were critical in the FDA's approval of REXULTI's indication for the treatment of schizophrenia in adolescents. The FDA's standard to establish safety and efficacy, particularly in connection with the review of an intended use in a non-adult population, underscores the nature and the importance of this new evidence. The regulatory approval addresses an important and significant unmet need. ICER's assessment of the evidence conflicts with FDA's assessment on the same evidence and does not reflect the importance of that regulatory assessment, or the value that it demonstrates. Moreover, the ability to treat adolescent patients with schizophrenia is particularly important. The risk–benefit profile of previously approved antipsychotics appears to be less favorable in adolescents with schizophrenia than adults, due to high rates of adverse events and treatment discontinuation. Consideration of the side-effect profile, which can differ substantially from medication to medication, is essential when choosing a treatment option in adolescent patients. Based on the interim analysis presented in Dragheim at al., (2021) REXULTI appears to be a well-tolerated treatment option for adolescents (aged 13–17 years) with schizophrenia, with a safety profile consistent with that observed in adult patients. Further, the initiation of treatment earlier in adolescence rather than adulthood, leads to better treatment and value gains for the patients, caregivers, payers, and society. A recent meta-analysis showed that early intervention for psychosis improved	After discussions with the manufacturer, ICER concludes that fewer than 10% of patients receiving Rexulti are adolescents and so evidence for this indication cannot be used as support for a price increase under the UPI protocol.

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	outcomes over time, including improved symptom severity and quality of life, reduced hospitalization, and better engagement with school and work. Therefore, the value of the new indication in an adolescent population provides additional value to the product beyond the initial indications, which has not been appropriately recognized by ICER and integrated into its value analysis.	
2.	Recent studies have further demonstrated that REXULTI is a safe, effective, high-value treatment in the real-world. Otsuka provided to ICER 14 additional scientific references to support the UPI review. These studies demonstrate that REXULTI improves clinical outcomes and patient quality of life, reduces medication discontinuation, reduces hospitalizations, emergency department (ED) visits and medical cost. The evidence package included 6 publications based on randomized clinical trials (RCT), a meta-analysis, 5 real-world evidence (RWE) studies, and 2 open-label studies, one based on a pharmacokinetic (PK) model. The studies represent just a sampling of the 144 publications and poster presentations identified in a targeted literature review of recent studies and analyses published between January 1, 2020 to March 31, 2022. These new clinical and research studies demonstrated that REXULTI improved clinical outcomes among patients with schizophrenia based on the PANSS scale, and among patients with MDD, based on the Montgomery- Asberg Depression Rating Scale (MADRS). Another study also found that REXULTI corrected circadian dysfunction in patients with MDD and inadequate response to antidepressant treatment. New evidence also demonstrated that REXULTI improved patient quality of life and reduced risk of discontinuation, a major and costly challenge in treating those patients. Two studies also demonstrated that REXULTI resulted in improved life engagement, while a third study demonstrated that REXULTI use in patients with MDD helped to reduce anxiety and lead to more calmness, a clinical finding with important implications in managing this difficult to treat and expensive condition. A RWE analysis also showed that the risk of discontinuing treatment among patients with MDD, a major challenge in addressing this condition, was lower for REXULTI compared to other atypical antipsychotics. In addition, a series of RWE studies have provided important evidence that use of REXULTI reduces health care resource utilization and medical costs relative to other atypical antipsychotics. For instance, unadjusted all-cause hospitalization (6.6% vs 12.5%) and ED visits (17.0% vs 27.5%) were lower with REXULTI compared to quetiapine extended release (XR) among patients with MDD. REXULTI-treated patients also had significantly lower mean medical costs ($6,421 vs $8,545, p=0.0123). Another study showed that psychiatric costs in patients with MDD using lurasidone or quetiapine were $1,662 and $3,894 higher than patients using REXULTI.16 Other studies consistently found that patients using REXULTI had lower psychiatric costs and reduced risk of psychiatric hospitalizations.	Please see GER 1a, 3b, 4b, and 5a.

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	These are substantial and important cost savings for both payers and society, which translate into clear and significant value. Perhaps most importantly, recent studies have shown that REXULTI is a cost-effective therapy. A study presented at the 2022 Annual Psych Congress found that, among patients with MDD with inadequate response to antidepressant therapy (ADT), adjunctive REXULTI was cost-effective vs. quetiapine XR 150 mg/day, quetiapine XR 300 mg/day, olanzapine/fluoxetine 12/50 mg/day, and ADT alone, at a willingness to pay of $100,000.18 This is substantial evidence and support of an economically justifiable price. Again, this is strong evidence of value and supports both a compelling clinical and cost-effectiveness rationale. ICER did not consider this piece of evidence when submitted. We urge ICER to modify the UPI assessment methodology to include more comprehensive value assessments, including cost-effectiveness modeling. Without doing so, ICER's conclusions are necessarily flawed and unreliable.	
3.	ICER's approach to drug pricing under UPI does not capture recent market conditions and does not accurately assess a drug's price or its value. ICER estimates of price increases are methodologically flawed. ICER stated that REXULTI took a 7.61% net price increase. However, the process by which ICER determined this net price increase is not transparent and is methodologically flawed. This assertion is incorrect. Because ICER's methodology is not transparent to us, we are not able to identify why and how the calculation fails to accurately reflect the product's net list price. ICER's statement that REXULTI's net price change resulted in $68 million in additional spending also is not accurate. The methodology relied on data from SSR Health, LLC. to estimate increase in net drug spending, but SSR Health's methodological approach suffers from measurement errors, given that, for some drugs identified through SSR Health's Rx Brand Pricing Data Tool, estimated net prices exceeded list prices. We do not believe ICER should use an estimate that is derived from such a flawed methodology. An alternative to consider would be taking a macroeconomic approach. Otsuka submitted an input-output price model that suggests a need to increase price of pharmaceuticals by 7.55% in response to changes in labor and capital costs of suppliers to pharmaceutical industry (Please refer to Otsuka's correspondence to ICER dated June 24, 2022 for the full model and report).	ICER gave Otsuka the opportunity to provide corrected net price evidence, but Otsuka opted to not do so.
4.	ICER's reliance on mCPI as price benchmark has significant limitations and is further evidence of a flawed methodology. ICER's reliance on medical consumer price index (mCPI) as a benchmark for the UPI ignores important market dynamics. Criticisms of the use of mCPI are extensively discussed in Berndt et al. (2000). Moreover, mCPI has not risen at the same rate as CPI in the past few years due to societal forces such as the COVID pandemic and the war in Ukraine. Rather than focus on mCPI, drug prices should be assessed under a broader lens capturing market dynamics to reflect the realities of bringing	ICER prespecifies a protocol and uses feedback from a panel of industry and insurance company representatives to share the protocol. We acknowledge that there is not one perfect source for inflation estimates, but that other health economists have recommended the use of medical CPI for the purposes of estimating the net present value of pharmaceutical prices.

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	drug products to the market during this rapidly inflationary period.	
5.	ICER's reliance on GRADE assessment is deeply flawed. ICER's reliance on GRADE to make assessments for the UPI is deeply flawed, as there are severe limitations in these tools. GRADE is subjective given the variability in the skills and training of raters creating significant low inter-rater reliability issues. GRADE is also not appropriate to evaluate individual studies. Further, GRADE is biased against observational studies. While RCTs have been considered the gold standard for assessing safety and efficacy of a drug, the trial designs often have strict inclusion and exclusion criteria. As such, the evidence derived during RCTs may not always be generalizable or representative of what occurs in real world settings once a drug is on the market. Therefore, observational studies should also be considered to assess effectiveness of a product in the real world. There is now growing evidence that the fidelity of results in an RCT can be reproduced in observational studies. Furthermore, FDA and the European Medicines Agency (EMA) have issued guidance for inclusion of real-world evidence for regulatory decision-making	We disagree with the characterizations of GRADE. On the specific issue of skills and training in using GRADE, we believe the ICER group working on the UPI report has adequate expertise in the application of GRADE.
6.	ICER should focus on a comprehensive assessment of value, rather than price in isolation. Otsuka submitted a catalog of evidence to support the clinical and economic value of REXULTI, including data from clinical trials, post-hoc analyses, RWE studies, and an updated cost-effectiveness analysis based on a prior model for REXULTI. However, ICER did not consider this evidence, but focused instead solely on the price increase in isolation. Otsuka recommends that ICER take into consideration a comprehensive view of value when assessing estimated price increases for products.	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.
	AbbVie	
1.	ICER incorrectly states Lupron's indication in the treatment of advanced prostate cancer and fails to recognize an updated use for Lupron during the phase of this assessment. As part of the evidentiary support for Lupron, AbbVie supplied ICER with the most current FDA approved label for Lupron which indicates that Lupron is now approved for the treatment of advanced prostate cancer, not the palliative treatment of advanced prostate cancer stated in the ICER report. This change signifies the ability for all advanced prostate cancer patients to potentially benefit from Lupron, in addition to patients no longer undergoing active treatment. ICER has failed to review the most current FDA approved label, thereby ignoring an advance in how Lupron could be used to treat advanced prostate cancer.	Thank you for this information. We have now updated the indication in our report.

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2.	ICER rejected two of the submitted studies as "low quality". However, ICER does not provide rationale for why the studies were deemed "low quality". • Vargas et al studied the impact of Lupron on height outcome in 48 patients with central precocious puberty (CPP) when treatment was initiated after chronological age (CA) of 7 years and continued beyond CA of 10 years or bone age (BA) of 12 years. The authors concluded that predicted adult height improved in most girls who initiated treatment after CA of 7 years. It continued to improve in most girls with longer treatment, even past BA of 12 years or CA of 10 years, which suggests that no absolute CA or BA limit should define initiation or end of treatment. Treatment plans need to be individualized, and neither treatment initiation nor cessation should be based on BA or CA alone. Within this pediatric area, this study with 48 patients was anything but undersized - in fact, it was a majority subset (87%) of the trial population which was accepted by the FDA for the approval of Lupron in the treatment of central precocious puberty. Moreover, this study was accepted and published by the peer-reviewed Journal of Pediatric Endocrinology & Metabolism, and thus offers objective scientific evidence for stakeholders. Yet, ICER rejected this study that a leading journal in the therapeutic area found scientifically credible, underscoring AbbVie's belief that ICER's UPI analysis is completely subjective and lacks scientific rigor. • Wallach et al was a retrospective study evaluating whether real-world data can be used to emulate the results of randomized clinical trials. The study used electronic health record and administrative claims data to emulate the ongoing PRONOUNCE trial (A Trial Comparing Cardiovascular Safety of Degarelix Versus Leuprolide in Patients With Advanced Prostate Cancer and Cardiovascular Disease). The study found that in 2,226 propensity score-matched patients with cardiovascular disease undergoing treatment for prostate cancer, degarelix was not associated with a lower risk of cardiovascular events than leuprolide. While this study was not a randomized clinical controlled trial, this study does represent the use of real-world evidence to understand the impacts of treatment, in alignment with the 21st Century Cures Act that among other intentions endorsed the importance of the use of real-world evidence. This study also aligns with the U.S. Food & Drug Administration and its published framework for its real-world evidence program that includes retrospective studies.	To clarify, the UPI analysis uses GRADE to assess the quality of the evidence and not the quality of the study. Please see GER 3b. Vargas et al. is an important paper that addresses treatment decisions in patients with central precocious puberty. However, it is a non-comparative observational study with a small sample size; therefore, using GRADE criteria, evidence of this sort is considered low quality in the absence of specific criteria that would increase the quality of the evidence. Wallach 2021 is a well-performed observational study conducted to compare the cardiovascular risk of leuprolide to degarelix. However, due to methodological limitations, including frequent crossovers between medications, missing data, and potential misclassification of endpoints, this study does not reliably and conclusively address the conflicting reports on the cardiovascular safety of gonadotropin-releasing hormone agonists compared with gonadotropin-releasing hormone antagonists. Therefore, using GRADE criteria, it is low-quality evidence from this trial for addressing a change in conclusion about what was previously believed. Also, please see GER 5a.
3.	It is also 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 on net price impact in their analysis. In ICER's published methodology for the UPI report, ICER states SSR Health net price data will be used to determine net price	ICER gave AbbVie the opportunity to provide corrected net price evidence, but AbbVie opted to not do so. Our understanding is that AbbVie raised concerns with SSR Health about their estimates and, in turn, SSR Health provided ICER with a manual flag around data quality concerns related to volume sold. ICER shared this information with AbbVie. This manual

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	impact. However, in the analysis for Lupron, IQVIA data is used – a deviation from ICER's protocol and another example where this analysis does not follow scientific principles. This action again highlights the subjective nature of the UPI report.	flag for data quality is not in ICER's protocol and therefore, under Section 8 of the protocol, ICER made the decision to use an alternative data source in this special case. ICER would have preferred to receive the accurate net price evidence from AbbVie. ICER does not wish to create an incentive for manufacturers who have accurate pricing and volume data to use information to undermine ICER's data sources without providing the corrected information to ICER and, as such, ICER is likely to take similar steps should this situation recur in the future.
	Ipsen	
1.	Increased Utilization: ICER's methodology for unsupported "price increase" measures Part B spend, not drug price. As the number of beneficiaries rises, so too does ICER's key evaluation metric. In this sense, ICER's assessment does not solely measure "price increase." In fact, demand for SOMATULINE DEPOT grew dramatically during the review period, with an additional 594 patients prescribed therapy in 2020. In total, $3.5M+ of the annual increase in Medicare Part B spend can be attributed to higher utilization driven by new SOMATULINE DEPOT patients and dose escalation, supported by the studies provided in Ipsen's June 24, 2022 response. ICER's report erroneously characterizes this growth in Medicare spend as increase in price.	Unfortunately, Ipsen has misunderstood ICER's methodology for selecting drugs within Medicare Part B. As the protocol states in Section 2.2.2-2.2.3, ICER isolates changes in spending per dosage unit to avoid the very issue that Ipsen raises (changes in utilization or volume). • 2.2.2. ICER will remove from the list any therapies that had an increase in average spending per dosage unit during the Medicare Part B Price Increase Period of less than medical CPI plus 2%. • 2.2.3. ICER will rank the therapies in the data set by the following algorithm: average annual total spending per patient in the first year of the Medicare Part B Price Increase Period multiplied by the percentage change in average spending per dosage unit (from first to last year of the Medicare Part B Price Increase Period) multiplied by the total number of patients who used the drug in the last year of the Medicare Part B Price Increase Period. This algorithm emphasizes changes in spending per dosage unit while not allowing for the estimate to be impacted by changes in patients who use the drug from one year to the next or by changes in level of use from one year to the next.
2.	Suspension of Sequestration: The percent change in average Medicare spending per dosage unit 2019-2020 was exacerbated by the suspension of sequestration from May 1, 2020 through the rest of that year. When sequestration was suspended, the average spending per dosage unit in 2020 increased. In this respect, the Part B spending from 2019 to 2020 was artificially increased.	Thank you for providing this context.
3.	Cost of Innovation: Despite its inclusion as allowable criteria, ICER did not consider the cost of innovation. Ipsen investment nearing $80M dollars for the current and next generation products demonstrates Ipsen's important critical commitment to discovering new uses of SOMATULINE DEPOT to help improve the lives of patients. Innovation is not free, and it is highly risky. Ipsen is proud of the investments it makes into research and	The inclusion is only as context that the manufacturer may provide. Manufacturers are given the opportunity to request that this information be reflected in the report, and Ipsen chose not to do so.

#	Comment	Response/Integration
	development. Any objective review of "supported" price/cost increases should acknowledge this connection.	
4.	We also want to reiterate concerns regarding transparent calculation of "unit price increase." With an appreciation for the fact that Medicare Part B data exists within the confines of the CMS system, Ipsen respectfully objects to the sole reliance by ICER on CMS figures which are not independently verifiable. Please see section 3.2 "Definition and Calculation of "Unit Price Increase" from Ipsen's initial response for additional feedback.	As stated in ICER's protocol, the CMS data are available to the public. • ICER will use publicly-available US government data to create a list of drugs covered by Medicare Part B that had average annual total spending (including Medicare payment, deductible, and coinsurance) of at least $50,000 per patient during the last year of the Medicare Part B Price Increase Period. Methodology of the Medicare Part B spending by drug dataset is found here. The protocol provides for manufacturers informing ICER if they have contested the Medicare results. If this does not seem a sufficient protection against inappropriate results or inclusion, ICER would appreciate thoughts on additional safeguards in future reports.
	Seagen	
1.	Seagen reiterates several concerns with the methodology that the Institute for Clinical and Economic Review (ICER) used in the selection and subsequent assessment of ADCETRIS in its report. Seagen's concerns with ICER's methodology include, but are not limited to, the limitations of Medicare data used in the analysis, the lack of transparency in assumptions related to patient cost burden, and most critically, the narrow, arbitrary, and unvalidated methodology employed to assess evidence. For example, ICER overlooked a key timeline of events related to the U.S. Food and Drug Administration (FDA) approval of ADCETRIS while rejecting key phase 3 data that demonstrated the value of the medicine. Specifically, ICER acknowledged that the ECHELON-2 study represented high-quality evidence that led to the FDA's November 16, 2018 approval of ADCETRIS for the treatment of CD30-positive peripheral T-cell lymphoma (PTCL). This approval was granted under the Real-Time Oncology Review (RTOR) Program and occurred less than 2 weeks after receipt of Seagen's complete program application, 20 weeks faster than the standard review timeline. Following the FDA's accelerated approval, the ECHELON-2 results were presented at the American Society of Hematology (ASH) annual meeting on December 3, 2018 with a subsequent print publication of the full data in 2019 in Lancet, a top-tier medical journal. In its assessment, ICER rejected this publication, claiming it did not provide new information since FDA approval occurred in November 2018, and not within their January 2019-December 2020 window. ICER's assertion suggests that a standard, unaccelerated FDA review period would have met ICER's review timeframe for this assessment. It was precisely the compelling nature of this data – which ICER itself acknowledged as high-quality before ultimately disregarding it – that precipitated approval of ADCETRIS under this accelerated timeline.	The UPI report has a specific timeframe. The reason is to be able to connect new evidence with price increases. A price increase occurring in 2020 can't reasonably be because of an indication approval that occurred three years earlier.
	Horizon	

#	Comment	Response/Integration
1.	Horizon is committed to developing therapies that can improve the lives of people living with rare diseases, and our recent research and development efforts for KRYSTEXXA epitomize this commitment. By limiting the presentation of data to 2019-2020, ICER's Unsupported Price Increase ("UPI") Medicare Part B assessment for KRYSTEXXA does not provide a complete view of the net health benefit of the use of methotrexate with KRYSTEXXA. Horizon's clinical research program studying the use of KRYSTEXXA with methotrexate began in 2019 and continued through 2022, ultimately demonstrating improved efficacy and safety that resulted in expansion of the FDA-approved label in July 2022 to include KRYSTEXXA co-administered with methotrexate. Yet, in its UPI Report, ICER declined to include any of the compelling data generated by Horizon over the last several years, and thus failed to capture the new clinical evidence supporting the benefit of KRYSTEXXA with methotrexate.	As stated in the protocol, the goal of the UPI report is not to perform full clinical and economic analyses on the therapies subject to the UPI analyses. Instead, the UPI report evaluates whether substantial new evidence (in the prior two years) exists that could justify the *current* price increase. The goal is to provide the public and policymakers with information they can use to advance the public debate on drug price increases.
2.	In the UPI 2022 Protocol, ICER states that Additional Drugs to be Reviewed include therapies heavily covered under Medicare Part B that have the potential to present a financial burden on individual patients. In this discussion, however, ICER does not acknowledge the large percentage of Medicare Part B fee for service (FFS) patients with supplemental coverage and only states that patients who pay coinsurance face a large financial burden. Although studies have indicated that use of coinsurance in the commercial market may create a financial burden for patients, different dynamics exist under Medicare Part B. Under Medicare Part B, the government pays 80% of the cost of Part B drugs while beneficiaries are responsible for the remaining 20%. An analysis from 2018 showed that 87% of patients that take Part B drugs have some form of supplemental coverage for the 20% cost share, including Medigap (or Medicare Supplemental), employer sponsored coverage, Medicare Advantage or Medicaid. The share of beneficiaries with FFS coverage and Medicare Supplemental coverage increased from 35% to 39% from December 2017 to December 2020. According to America's Health Insurance Plans (AHIP), "only 4% of enrollees with Medicare Supplemental coverage reported having difficulty paying medical bills in the last 12 months." Horizon respectfully requests that ICER acknowledge the role supplemental coverage plays in affordability for beneficiaries with Medicare Part B FFS coverage when publishing the final report to provide a more holistic discussion of the stated purpose of the new list.	Supplemental coverage pays portions of this 20% responsibility. That is true. However, it is also true that the premiums for the supplement insurance continue to rise given that this insurance is optional and therefore, the enrollees are indirectly paying for the 20% coinsurance whether it be out of pocket or through their premium increases in supplemental insurance. It is correct that not all patients pay 20% coinsurance by virtue of having purchased supplemental coverage. It is for this reason that we discuss the individual coinsurance payments in language of being "up to" 20% of the list price of the drug. Additionally, however, increases in list prices of course result in higher individual premiums for supplemental insurance making the supplemental insurance itself less affordable.
3.	ICER's Determination Does Not Reflect the Overall Clinical Value of New Evidence Supporting KRYSTEXXA In an effort to improve both safety and efficacy, Horizon initiated a series of studies on the use of immunomodulators with KRYSTEXXA to prevent or minimize ADA development. Horizon's clinical research program for KRYSTEXXA with immunomodulation as co-therapy started in 2019, concluded in October 2021, and culminated in July 2022 with the expansion of the FDA-approved label for KRYSTEXXA to include co-administered with methotrexate. Thus, the FDA's approval of	Please see GER 1c and 5a.

#	Comment	Response/Integration
	KRYSTEXXA with methotrexate represented the culmination of years of effort and demonstrates Horizon's commitment to working together with the gout community to improve both patient experience and clinical outcomes. The results from these studies were first made available in 2019 and 2020 and submitted to ICER as new evidence of clinical safety and effectiveness. The evidence submitted on the use of immunomodulation (comprising methotrexate, mycophenolate mofetil, azathioprine and leflunomide; total of 72 patients) was compelling and suggested a response rate of 60% to 100% (an increase from 42% from the registration trials) with a reduction in the frequency of infusion reactions. Since 2020, a number of these studies have been published in peer-reviewed journals. Data on immunomodulation with KRYSTEXXA led to increasing adoption of concomitant administration of KRYSTEXXA with immunomodulation by the clinical community in the treatment of patients with uncontrolled gout (from 1 – 4% in 2015 to 15% in 2019 and 16.8% in 2020). Based on the scientific evidence supporting the use of immunomodulation with KRYSTEXXA generated in 2019 and 2020, Horizon launched the MIRROR RCT—Methotrexate to Increase Response Rates in Patients with Uncontrolled Gout receiving KRYSTEXXA—results from which ultimately supported the label expansion for KRYSTEXXA. MIRROR RCT evaluated the safety and efficacy of oral methotrexate (MTX) as co-therapy with KRYSTEXXA in patients with chronic refractory or uncontrolled gout (N=152). The primary endpoint (proportion of patients who achieved sUA <6 mg/dL for ≥80% of time during Weeks 20–24) was achieved in 71.0% of patients on KRYSTEXXA + MTX versus 38.5% of patients on KRYSTEXXA alone (p<0.0001). The incidence of new ADA formation was reduced with co-administration of methotrexate, resulting in higher KRYSTEXXA exposure and lower infusion reaction occurrence in patients co-treated with methotrexate (4.2% [includes 1 case of anaphylaxis based on NIAID/FAAN criteria]) than those receiving KRYSTEXXA alone (30.6%). The MIRROR RCT results thus reinforced the substantial body of data supporting the use of KRYSTEXXA with immunomodulation, which also includes the open-label studies discussed above and RECIPE (a Phase 2 randomized, double-blind, multicenter study evaluating the addition of mycophenolate mofetil to KRYSTEXXA)—all of which were submitted to ICER as new evidence.	
4.	The rationale behind ICER's decision to exclude 8 publications supporting use of immunomodulation with KRYSTEXXA from consideration in the UPI Report on the basis that they involve an "intervention/comparison not relevant to scope" or "outcomes not relevant to scope" is unclear and contradictory. As a threshold matter, it is difficult to understand how studies demonstrating improved efficacy and safety of KRYSTEXXA via concomitant use of an immunomodulatory agent would be considered outside the scope of an assessment intended to ascertain the value of KRYSTEXXA. These studies have already prompted a shift in the treatment paradigm for uncontrolled	Please see GER 1c and 5a.

#	Comment	Response/Integration
	gout, confirming the value of this evidence to the medical community. Further confounding the assessment, ICER does not appear to apply a consistent methodology for determining which evidence is in- versus out-of-scope. Although ICER's assessment criteria provide that ICER may exclude a given study for "multiple reasons," additional reasoning is not explained in the final report. For example, ICER apparently did accept one publication on the use of methotrexate with KRYSTEXXA as "in-scope," yet provided no rationale for excluding others that may have met the UPI criteria.	
5.	In addition to the clinical evidence supporting the use of immunomodulation with KRYSTEXXA, Horizon has prioritized research investigating comorbidities associated with gout. Hypertension, diabetes, chronic kidney disease and cardiovascular disease are commonly associated with gout, with a higher prevalence of these conditions in gout patients and an even higher prevalence in uncontrolled gout patients.36-38 We are actively analyzing the KRYSTEXXA data to help clinicians understand the added benefits of KRYSTEXXA therapy among patients with comorbidities, including hypertension control, hepatic fibrosis and use in patients with renal disease.	Please see GER 1a, 1b, and 5a.

Appendix P. Manufacturer Comments

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

Bausch Health is committed to continued research across our portfolio with the goal of providing the clinical and health economic data that allows for informed decision making by our stakeholders. This, in tandem with our commitment to maximize affordable access to our therapies, 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 the 2020 and 2021 Unsupported Price Increase (UPI) cycles where we provided 28 and 25 peer-reviewed publications, respectively. We believe these studies systematically demonstrated the clinical and economic value of Xifaxan in HE and IBS-D, but they were disregarded by ICER. As noted in our 2020 and 2021 response during Manufacture Input Phase II, we continue to disagree with ICER that the inclusion/exclusion methodology and rationale provided by ICER which disregards critical peer-reviewed evidence and provides an incomplete picture of Xifaxan's value for U.S. patients and payers.

For the 2022 Manufacturer Input Response Phase II, Bausch acknowledges that ICER's search identified 18 articles of which one was screened as full text. However, the remaining 17 unscreened full text articles by ICER may contain valuable information in the body of the manuscript but not reported in the abstract. We would like to note that the Abdel Moneim M et al. 2021[1] 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 the difference in minimum inhibitory concentration of rifaximin of intervention v. control) was not significantly different amongst those in the rifaximin group (v. lactulose alone). However, they did report that those in the rifaximin group had significantly lower risk of developing HE and the time to the first episode of the 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. While the dose used in the study (i.e., 400 mg rifaximin 3 times daily) and the on-label study population does not conform to the FDA-approved Xifaxan label for HE, the study does show rifaximin's value in terms of a lower risk of the development of an HE episode and the time to an HE episode in line with the FDA label.

Additionally, in your review the Patel VC et al.[2] study was identified in your search, however, not screened as full text. This study found that amongst patients with cirrhosis and HE treated with rifaximin 550 mg, though the primary endpoint was not achieved (i.e. did not achieve 50% reduction in neutrophil oxidative burst at 30 days from baseline), at day 30 and 90 day from treatment initiation, the grade of HE normalized which is generally supportive of the "reduction in risk of breakthrough HE episode" seen in the pivotal trial for Xifaxan 550 mg (section 14 of FDA label). Failure to achieve the primary outcome in this study does not imply lack of efficacy, but rather points to a different mechanism by which rifaximin exerts its effects. The exclusion of critical evidence that supports Xifaxan's value further highlights our concerns with ICER's scientific rigor in identifying/critiquing this critical evidence.

What we want to highlight is ICER's assessment of the Jesudian AB, 2020[3] study during the 2020 and 2021 UPI cycle. Bausch had provided the Jesudian AB, 2020 (cost-effectiveness evidence) to support the value of XIFAXAN in HE for the 2020 and 2021 UPI. ICER deemed the study as "Study published outside of the timeframe of our review" for 2020 UPI and as "Previously known information about rifaximin related to cost" for 2021 UPI. We had disputed this characterization of this study in our 2021 Manufacturer Input Phase II response with details of why the study evidence supports and augments the value of XIFAXAN.

In the final report posted by ICER on November 16, 2021, ICER stated: *"We agree that Jesudian does potentially provide new information related to cost and we have reviewed it"*. However, you dismissed the study stating: *"Economic models rarely provide high or moderate-quality evidence by GRADE criteria, and that matches with our conclusion about Jesudian."* Further, in your response you concluded that the Jesudian AB, 2020 did not provide high or moderate-quality evidence of a substantial benefit that was not previously known by stating: *"**As an example, the model in Jesudian assumes mortality benefits based on a single-arm, open-label study. Mortality is clearly central to the modelling and yet the evidence for effects on mortality is of low (or very low) quality**."* We disagree with your methodology in characterizing this evidence supporting Xifaxan's value.

Before the Jesudian AB, 2020 study was sent to the Journal of Managed Care & Specialty Pharmacy for publication, we had conducted the following:
1) a targeted literature review to identify relevant articles that reported mortality among hospitalized and not hospitalized HE patients in the U.S.;
2) critically evaluated quality (using RoB 2 tool, ROBINS-I checklist, and STROBE framework, as applicable[4,5,6]) of the relevant identified studies in step 1, and
3) scenario analysis to:

a) evaluate the impact of assuming no mortality benefit associated with XIFAXAN; and
b) evaluate the impact of assuming mortality benefits from studies conducted/published after Jesudian AB, 2020.

The targeted literature review identified 19 studies of which only four studies were relevant to the U.S. population. Of these four relevant studies, Landaverde et al. 2020[7] and Bajaj et al. 2019[8] were published after the Jesudian AB, 2020 study (2018-2019) was conducted; and Courson et al. 2016[9] reported mortality among hospitalized patients only. Hence, at the time when the Jesudian AB, 2020 study (2018-2019) was developed, only Mullen et al. 2014[10] was the best available source of mortality rates among non-hospitalized patients in the U.S. The Jesudian AB, 2020 study team was fully aware of the quality of the Mullen et al. 2014 study and thus validated the mortality rate obtained from Mullen et al. 2014 with Bannister et al. 2016[11], a high-quality study that reported mortality rates among non-hospitalized patients in the United Kingdom. The mortality rates obtained from both studies were similar, hence estimates from the Mullen et al. 2014 were used as this was from the U.S. population. Though it can be reasonably concluded that the study by Mullen et al. 2014 is of low quality, the results from the study are likely to be

valid in the US context based on validation with Bannister and was the best available data at the time of the Jesudian AB, 2020 study was conducted and published.

Further, in our scenario analysis, we assessed the impact of removing mortality benefits associated with rifaximin from the model as well assuming mortality benefits from studies conducted/published **after** the Jesudian AB, 2020 study. Based on the scenario analysis results (Table), it can be concluded that the mortality benefits associated with rifaximin are likely to have little to no impact on the cost per QALY gained for rifaximin as it remained under $30,000 per QALY gained under alternate scenarios (scenarios 1-3). Further, using mortality estimates from Landaverde et al. 2020 (scenario 4) and Bajaj et al. 2019 (scenario 5) would not significantly change the ICER results in the Jesudian AB, 2020 study.

Table. Scenario Analysis using available U.S. mortality data identified from literature review (updated as of October 12, 2022)

Scenario	Description	ICER (cost per QALY gained) [$]
	Base case reported in the Jesudian et al. 2020[3]	$29,161
1	Two weeks mortality after hospitalization for rifaximin + lactulose arm is assumed to be same as lactulose arm (0.9%)[10]	$29,163
2	In-hospital two-week mortality during HE hospitalization for rifaximin + lactulose arm is assumed to be the same as lactulose arm (49.1%)[12]	$29,912
3	Scenario 1 AND 2	$29,914
4	Mortality rates from Bajaj et al. 2019[8]	$29,244
5	Mortality rates from Landaverde et al. 2020[7]	$29,149 - $29,155*

HE: hepatic encephalopathy; ICER: Incremental cost-effectiveness ratio; QALY: quality-adjusted life years/* ICER range corresponding to the mortality rates from 6 and 12 months, respectively/[$] Reported as 2018 dollars

Hence, ICER's assumption and assessment of *"Mortality is clearly central to the modelling and yet the evidence for effects on mortality is of low (or very low) quality"* is a misinterpretation of the evidence submitted by Bausch. We would have gladly provided this information before November 2021 if ICER had asked for it. It is regrettable that ICER did not reach out to Bausch over the two years for this evidence and erroneously concluded that the Jesudian AB, 2020 is of poor quality. This is one of the reasons we are unsure if actively engaging in ICER's UPI process provides the most robust/transparent scientific interactions for our patients and payers.

We would like to reiterate our concerns regarding ICER's assessment of XIFAXAN and the rationale and decision making on ICER's inclusion/exclusion criteria for the assessment of critical peer-reviewed evidence that provides an incomplete picture of Xifaxan's value. We feel strongly that ICER's search strategy outlined in section 4.1 of the Overview of Review Process (subsection 4.1.2) of the UPI Assessment protocol for identifying "new information" on benefits and harms during the evidence review period is restrictive, narrow, and vague. Specifically, per your protocol, ICER performs "independent systematic reviews" focused on identifying new information from randomized controlled trials (RCTs) only. Furthermore, your protocol states that ICER will not independently look for information other than RCTs but will assess RCT and non-RCT information published or presented during the evidence review period that is submitted by manufacturers. ICER's "independent systematic reviews" focused on identifying new information only from RCTs only and basing the assessment primarily on evidence from RCT discounts new information that can be supported by non-RCT data (e.g., real-world evidence, economic models, etc.)

The Volk ML, 2021[13] study submitted by Bausch during the UPI 2020 and 2021 cycles was deemed as "Study published outside of the timeframe of our review" by ICER. The Volk ML, 2021 study is the most recent and relevant U.S. real-world evidence available that highlights the reduction in healthcare utilization and costs associated with the use of and adherence to Xifaxan (v. lactulose alone) amongst patients with HE. The Volk ML, 2021 study findings have been central to payer interactions and have enabled several payers to make clinically appropriate decisions on Xifaxan coverage for patients with HE. Dismissing key pieces of recent and relevant evidence due to the restrictive evidence review period and search strategy trivializes the evidence supporting the value of Xifaxan. If you have a meaningful scientific critique of the Volk study, we would be glad to address it, but not engaging with Bausch and dismissing it in your final report would continue the same pattern as you have done with the Jesudian AB study, potentially diminishing 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 recent and relevant studies which provides U.S. payers and patients relevant insights into the true value of Xifaxan, yet are categorized as "outside of the time frame." We are also disappointed with the way ICER evaluates our published evidence, draws erroneous conclusions, and publishes unsubstantiated conclusions without making an effort to follow up with Bausch for clarifications on submitted evidence, in spite of the approximate 9-month ICER UPI engagement timeframe.

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Amgen appreciates the opportunity to respond to ICER's Unsupported Price Increase Report (UPI): Preliminary Assessment of Prolia® (denosumab). Amgen believes that an incorrect assessment of net price increases and other methodological shortcomings led ICER to include Prolia in its analysis. Additionally, due to its limited outlook on patient preferences, ICER disregarded relevant evidence reinforcing the value of Prolia.

Prolia is proven to significantly reduce the incidence and risk of vertebral, hip, and nonvertebral fractures at 3 years in postmenopausal women with osteoporosis.[1] Unlike oral bisphosphonates, which have plateauing effects at 3 years, Prolia significantly increases bone density at the hip and sustains low fracture rates for *up to 10 years*.[2] Prolia has demonstrated superior efficacy in increasing bone density vs. alendronate, a strong safety profile, and cost-effectiveness. Additionally, the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) recommend Prolia for first-line treatment in post-menopausal osteoporosis patients at high risk of fracture.[3,4,5,6,7] Although osteoporosis has a high prevalence rate and well-defined patient population, treatment rates since 2013 have fallen due in part to a reduction in diagnosis and appropriate, timely care, meaning more patients have suffered from avoidable fractures.[8,9] This trend is concerning due to the debilitating impairment that can be associated with fractures as well as their financial burden, with initial fracture care costing between $13-$44K, and doubling or tripling with subsequent fractures.[10,11] Prolia can help protect against osteoporosis-related fractures and their related costs.

ICER has failed to follow its own methodology by disregarding the evidence base supporting the value of Prolia and new research that indicates superior treatment persistence. ICER's UPI protocol specifically solicits, *"New evidence or analyses published or presented over the two-year Evidence Review Periods that* ***demonstrate improved clinical or economic outcomes*** *compared with what was previously believed,"* and notes, *"****Studies reporting patient-reported outcomes****…will be highly relevant."* Singer *et al*. **demonstrated new evidence** of improvement in the **patient-important outcome** of persistence, yet ICER subjectively discounted this evidence as being unsupportive. Though previous recommendations and a majority of Amgen's submitted evidence pieces were overlooked, we will reiterate the following recommendations:

1. **Use more accurate data sources: net price data sourced exclusively from SSR health has many limitations, particularly for physician-administered drugs like Prolia.**
2. **Rate the results from the Singer *et al*.[12] study as <u>high-quality</u> evidence as these results directly translate to patient-important outcomes.**
3. **Incorporate direct drivers of the U.S. healthcare system into the UPI report.**

Below, we outline these recommendations in more detail.

Recommendations

1. Use more accurate data sources: net price data sourced exclusively from SSR health has many limitations, particularly for physician-administered drugs like Prolia.

ICER's use of SSR Health data incorrectly overestimates the net price change of Prolia. ICER's inclusion of Prolia in this report is based on pricing figures from SSR Health, a source inappropriate for ICER's net price calculations, which Amgen has previously brought to ICER's attention. SSR Health's use of averaged inputs compromise the reliability of price estimates. Furthermore, SSR Health is a far less accurate choice for physician-administered drugs like Prolia due to its limited capacity to record volume units and use of volume data from Symphony Health, which specializes in *retail* pricing data. Although ICER stated that Amgen did not offer alternative data, Amgen did in fact provide a more accurate net price calculation which was significantly lower than the estimate from SSR Health. This figure was derived from IQVIA, which boasts audit-level detail on 97% of *non-retail* U.S. drug sales. IQVIA is a trusted data source and the industry standard for critical business proceedings, making it a valid proxy for proprietary internal data. However, ICER rejected the lower, more accurate net price figure from IQVIA and persisted in citing SSR Health's steeply overestimated net price change.

2. Rate the results from the Singer *et al.*[13] study as high-quality evidence as these results directly translate to patient-important outcomes.

Patient-important outcomes are widely understood to include any variables that "*reflect how a patient feels, functions, or survives*."[14,15] Persistence *is* a patient-important outcome: persisting with treatment leads to lower fracture rates resulting in patient avoidance of significant physical pain, preservation of independence, and prevention of stress from post-fracture care and rehabilitation.[16,17,18,19] Improvement of patient-important outcomes is a key driving force in Amgen's research, and we believe evidence that is meaningful to patients is of the highest value. Amgen submitted four evidence sources that fulfill this criterion, yet ICER only accepted one and then discredited the outcomes of this study. Singer *et al*. demonstrate from claims data that Prolia users persisted longer with treatment than patients taking other anti-resorptive medicines, including oral bisphosphonates.[20] In spite of the study's rigorous design and well-characterized sample population, ICER rated it as "*low"* quality evidence for having *"uncertain"* effects on patient-important outcomes. This directly contradicts a strong body of evidence connecting treatment persistence to patient-important outcomes; multiple studies show that persistent osteoporosis medication use correlates with greater reduction of fracture risk, significantly lower total healthcare costs, and reduced bone loss, all of which are immensely valuable to patients.[21,22,23,24,25] This makes clear that the higher persistence of Prolia in the Singer *et al.* study translates to greater overall benefits for patients.

Rejecting this evidence for *"indirectness"* diminishes the patient experience and fails to account for its manifold and interconnected elements. It is crucial that payers and policymakers consider the patient journey more deeply before accepting vague dismissals of high-quality

evidence. Value assessment works against its design when it results in policies that exacerbate undertreatment, which is a significant problem in osteoporosis. A recent global study showed that between 2005-2018, the number of hip fractures per 100,000 individuals in the U.S. was nearly double that of the U.K. and over five times the rate in Japan.[26] This is concerning given that postmenopausal women experiencing a fracture have a 10% risk of another fracture within one year, contributing further to decline in function, diminished quality of life, and higher morbidity.[27,28] Additionally, while treatment rates within one year of fracture were down only 8% in the U.K. and up 11% in Japan (2013 to 2018), the U.S. *saw a 31% decline*, suggesting a disproportionate national shortfall in diagnosis and care.[29]

Without sufficient improvements in diagnosis and treatment, osteoporosis-related fracture care in the U.S. is projected to cost $95.2 billion annually by 2040.[30] To reduce this immense economic burden and, more importantly, to relieve the degraded quality of life associated with osteoporosis, it is essential that non-restrictive coverage policies give patients a choice in their treatment options. Utilization management barriers also have broad implications on health equity and treatment gaps. Evidence suggests that non-Hispanic Black women have lower screening rates, higher rates of discharge without rehabilitative care, and 225% higher post-fracture destitution (*i.e.*, becoming Medicaid dependent) than non-Hispanic white women.[31] Improved access to osteoporosis diagnosis and treatment needs to be prioritized to close these gaps.

3. Incorporate direct drivers of the U.S. healthcare system into the UPI report.

Currently, ICER's methodology solely targets perceived budget impact and estimated net price change based on third party extrapolations. Public debate about the cost of medicines often focuses solely on the list price and does not account for the amount or quality of coverage, the rebates, or the discounts that are negotiated between a complex array of wholesalers, distributors, pharmaceutical benefits managers (PBMs), health plans, providers, and other entities.[32,33] ICER's methodology does not recognize the complexity of the U.S. healthcare system (*e.g.*, private and public state-specific systems with differing utilization patterns) or the influence of various third parties in payer contracts.[34,35,36] In order to preserve patient access, negotiating formulary position is crucial, as both payers and PBMs impose high patient cost-sharing, establish utilization management barriers, or outright deny coverage if a drug is off-formulary or on a non-preferred formulary tier.[37]

ICER's UPI report does not measure impact on patient-important outcomes such as reduced fracture rates nor does it capture associated patient out-of-pocket cost-savings. ICER provides no discussion of the real-world value Prolia brings to patients and the health system. Given the complexity of real-world drug pricing, ICER's UPI methodology has many limitations. It is crucial that ICER takes a broader, all-encompassing approach that recognizes U.S. healthcare's complex underlying relationships and promotes coverage breadth and depth.

Conclusion

Amgen continues to invest in high-quality patient-important outcomes research and believes that Singer *et al.* provides compelling evidence of patient benefit. Three other studies were submitted that also support the value of Prolia to patients, insurers, and healthcare providers, but ICER excluded these due only to the UPI report's narrow and arbitrary timeframe. Concerningly, ICER did not acknowledge the impact of COVID-19 during this same timeframe. It should be recognized that the pandemic affected all segments of the economy including research. COVID-19 also affected the medical care consumer price index (CPI) which ICER uses to refine its list of drugs for review; the unadjusted medical CPI for this year's report (2021 relative to 2020) was only 1.2%, whereas the average medical CPI using unadjusted rates for 2020 relative to 2019 was 4.1%, and 2.8% for 2019 relative to 2018. In consideration of the extraordinary circumstances of COVID-19, ICER should adjust its evidence timeframe and use the previous year's medical CPI; failing to do so brings the validity of ICER's report into question as it may misrepresent product value, cost-offsets, and market drivers. Lastly, we recommend that ICER utilize more accurate data sources like IQVIA and recognize the complex underlying relationships that are at play within the U.S. healthcare system. These changes will help ICER achieve a more comprehensive report that reflects the true treatment landscape and the value of Prolia to patients.

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Takeda Response to ICER's Unsupported Price Increase Preliminary Assessment of Vedolizumab

October 26, 2022

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RE: Takeda Response to ICER's Unsupported Price Increase (UPI) Preliminary Assessment

Submitted electronically via: publiccomments@icer-review.org

Dear Dr. Pearson:

Takeda appreciates the opportunity to respond to ICER's draft Entyvio UPI report. Takeda Pharmaceutical Company Limited (Takeda) is committed to bringing better health and a brighter future to patients by translating science into highly innovative medicines. Recognizing the unmet need for managing chronic gastrointestinal diseases, Takeda has developed Entyvio® (vedolizumab), a humanized monoclonal antibody that is an α4β7 integrin receptor antagonist approved in 2014 for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) and Crohn's disease (CD), for both biologic naïve and tumor necrosis factor alpha (TNFα) antagonist failure patients. The clinical development program included three large, multicenter, randomized, double-blind, placebo-controlled studies (GEMINI 1, 2, 3) and one open-label Phase 3 extension study, followed by an extensive series of additional clinical trials and real-world studies. [1,2,3,4,5] Entyvio's mechanism of action, demonstrated efficacy, safety, and long-term durable clinical remission translate to positive treatment benefits for adult patients with moderately to severely active UC and CD.

Takeda maintains that the draft ICER report inadequately reflects the value and benefit of vedolizumab to patients with inflammatory bowel disease (IBD) that has been established and reinforced through continued research with clinical trials and real-world studies. We would like to offer the following feedback regarding ICER's 2022 draft Entyvio UPI report for your consideration:

Recommendation: validate and contextualize price increases

Takeda is dedicated to improving patient health, and thus prices medicines in a way that makes them accessible to as many patients as possible, while recognizing the value they bring to patients, providers, and the overall healthcare system. In alignment with Takeda's pricing philosophy, over the last few years our annual gross and net price changes across our United States portfolio have

been and continue to be single digit increases. ICER typically leverages net prices estimated from the SSR Health database, yet these are not validated, are often inaccurate, and consequently, may overestimate the real-world costs of drugs in IBD, including vedolizumab, paid by various plans. Takeda appreciates that ICER's draft report has cited the net price change that was shared with them, yet remains concerned with ICER's default use of the SSR Health database.

Additionally, ICER notes that total market expenditure of vedolizumab increased over this time in order to highlight the impact of the price increase. However, total expenditure reflects both price and overall volume of use. Prescribing trends over the time period of the evaluation have demonstrated an increase in overall advanced biologic utilization, as well as an increase in use of vedolizumab compared to biologic medication options. We attribute this increase in uptake to revealed perception of value. This factor alone has an intuitive impact on overall expenditure, and it seems discrepant for ICER to interpret this with a negative lens rather than as an indication of value.

Recommendation: consider the full extent of clinical data

As part of the assessment, ICER aims to review new evidence for vedolizumab over the prior year. However, ICER continues to have opaque methodology, with subjective assessment of the magnitude of clinical effects demonstrated by new evidence, limited detail provided regarding why a study's outcomes are considered irrelevant, and exclusion of studies that add to a comprehensive body of evidence. For example, ICER explicitly rejects any evidence for indications composing less than 10% of the treated population, yet these smaller populations are important to consider in aggregate. There is high value to including studies with smaller subgroups in IBD, specifically, due to the heterogeneous and chronic nature of the disease. The diversity of clinical presentation is so wide that looking at subgroups is how we share with providers information on where vedolizumab's effect is highly significant.

As part of Takeda's emphasis on meeting an unmet need in IBD, there has been a continued commitment to generating scientific data and publishing high-quality, rigorous clinical trials and real-world data to identify the optimal use of vedolizumab for patients. Well over 100 clinical trials and observational studies of vedolizumab use in UC and/or CD have been published over the years including key studies such as the GEMINI trials, [1,2,3,4,5] VARSITY trial, [6,7] and VICTORY consortium, [8,9] as well as the EARNEST and ENTERPRISE randomized-controlled trials (RCTs).[10,11] Additionally, real-world studies such as EVOLVE, RALEE, and ROTARY, are among other ongoing studies that provide additional insight into the clinical effectiveness and safety of vedolizumab.[12,13,14,15,16]

Takeda Response to ICER's Unsupported Price Increase Preliminary Assessment of Vedolizumab

Takeda previously provided a selection of references including recent RCTs and real world studies for ICER's consideration. Among these, ICER rejected information from the EARNEST trial (Travis et al 2021) as pertaining to a small population, yet this led to the European Commission expanding vedolizumab's approved indications – a demonstration of recognized value. Additionally, information that ICER deems "previously known regarding efficacy and safety" bolsters physician and patient understanding of who will benefit clinically from using vedolizumab, and thus enhances the picture of overall value. As noted above, prescribing trends have shown increased use of vedolizumab over the time period considered, thus indirectly indicating the perception of benefit within the healthcare system. Therefore, Takeda recommends that ICER consider all new published evidence, even those that impact smaller populations or reinforce understanding of benefit.

In conclusion, a thorough and comprehensive assessment of the value of vedolizumab should take into consideration the previously provided clinical evidence that demonstrates and confirms efficacy, safety, and durability of treatment over time. Assessing the magnitude of benefit within the therapy area should be transparent and performed in collaboration with IBD experts. And finally, ICER's assessment should incorporate the most up-to-date and accurate price considerations.

UC and CD are chronic and heterogeneous conditions requiring a personalized approach to treatment. ICER should leave treatment options to patients and clinicians treating IBD, based on comprehensive evidence and medical guideline recommendations. It is important to preserve access to all therapeutic options for patients and guide treatment selection with solid evidence that is based on sufficient term of follow-up. We appreciate the opportunity to share insights and welcome further discussions. Ultimately, Takeda seeks to see that all products assessed are evaluated according to their full holistic value to patients and society, and Takeda supports appropriate analyses that incorporate elements that are important to patients and reflect real-world clinical practice.

Kind Regards,

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October 26, 2022

Steven D. Pearson, MD, MSc, FRCP
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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 2020-2021. 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 REACH2 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] This evidence led to a new FDA-approved indication and multiple Category 1 upgrades 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 the data from RESPONSE, RESPONSE2 and JUMP demonstrate only "previously known information about ruxolitinib related to efficacy" and that the real-world evidence (RWE) studies constitute "low-quality evidence."[4,5,6] These trials provided clinically meaningful long-term efficacy and safety data that help inform the benefit-risk profile of Jakafi. Further, our RWE studies have been recognized by the scientific community at global scientific congresses and in peer-reviewed hematology journals.[7,8,9] Importantly, the studies described the impact of treatment with Jakafi on overall survival in MF in the post-approval setting and demonstrated 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. During 2020-2021, Incyte invested more than $2.5 billion in research and development, which equated to nearly 50% of Incyte's total revenues during this period. This level of R&D investment is double that of the industry average of about 25% of revenues.[10]

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. The price of Jakafi is in the lower third of oral oncology monthly cost of therapy, and insurance companies support the use of Jakafi with ≥ 97% of covered lives with access to 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

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Head of Market Access, Distribution and Patient Access Services
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Otsuka

October 26, 2022

RE: ICER's Unsupported Price Increase Assessment for REXULTI® (brexpiprazole)

This letter responds to ICER's preliminary Unsupported Price Increase (UPI) assessment of REXULTI® (brexpiprazole). As noted in our prior correspondence, REXULTI produces high value to patients, clinicians, payers, caregivers, and society. Price changes in the review period are reasonable and justified, especially given the substantial current trends in inflation. With regard to the core questions of whether a reviewed product has generated new evidence in support of its value that add to the clinical rationale for the product, REXULTI has, in fact, generated substantial new evidence that has successfully supported an expanded Food and Drug Administration (FDA) indication addressing an important unmet need:

- During 2021, new clinical evidence supported the FDA approval for an expanded indication for patients aged 13-17 with schizophrenia.
- Recent, new evidence has demonstrated that REXULTI is a safe, effective, cost-effective, high-value treatment for patients with schizophrenia and major depressive disorder (MDD). Significantly, both conditions have large populations that, if left untreated or treated inadequately, create significant costs for payers and society at large.

Although most of this letter addresses the issue of new clinical evidence and a strong clinical rationale for REXULTI, we do feel compelled to repeat some of our earlier concerns about the flaws in ICER's methodology. ICER's approach to drug pricing under UPI does not capture recent market conditions and does not accurately evaluate a drug's price, or its value.

Below, we present our new evidence and our objections to ICER's conclusions.

New clinical evidence has recently supported an important expanded indication demonstrating the clinical benefit of REXULTI for patients aged 13-17 with schizophrenia.

While ICER claims that there is limited and low-quality new evidence to support changes in REXULTI's price, FDA granted a new indication for REXULTI in December 2021 based on the evidence submitted to ICER. Dragheim at al. (2021) reported that adolescent patients with schizophrenia showed sustained improvement in the Positive and Negative Symptom Scale (PANSS) Total score from baseline to Month 12 and to last visit during treatment with REXULTI. The mean change in PANSS Total score from baseline to

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last visit was -14.8 (80.5 vs. 65.7).[1] This change in PANSS Total score in adolescents was similar to that seen in adults.[2-3]

The analysis by Kalaria et al. (2020)[4] further provided the basis for extrapolating the efficacy of second-generation antipsychotics from adults to adolescents. It quantitatively justified the similarity in placebo response and exposure–response between adults and adolescents in the treatment of schizophrenia.

In Wang et al., an Otsuka-led analysis using aripiprazole adult and adolescent data further confirmed the key features of the efficacy extrapolation in Kalaria et al. and extended the analysis to REXULTI. The model predicted efficacy in adolescents. This provided additional support for the extrapolation of REXULTI's efficacy from adults to adolescents.[5]

These results were critical in the FDA's approval of REXULTI's indication for the treatment of schizophrenia in adolescents.[6] The FDA's standard to establish safety and efficacy, particularly in connection with the review of an intended use in a non-adult population, underscores the nature and the importance of this new evidence. The regulatory approval addresses an important and significant unmet need. ICER's assessment of the evidence conflicts with FDA's assessment on the same evidence and does not reflect the importance of that regulatory assessment, or the value that it demonstrates.

Moreover, the ability to treat adolescent patients with schizophrenia is particularly important. The risk–benefit profile of previously approved antipsychotics appears to be less favorable in adolescents with schizophrenia than adults, due to high rates of adverse events and treatment discontinuation. Consideration of the side-effect profile, which can differ substantially from medication to medication, is essential when choosing a treatment option in adolescent patients. Based on the interim analysis presented in Dragheim at al., (2021)[1], REXULTI appears to be a well-tolerated treatment option for adolescents (aged 13–17 years) with schizophrenia, with a safety profile consistent with that observed in adult patients. Further, the initiation of treatment earlier in adolescence rather than adulthood, leads to better treatment and value gains for the patients, caregivers, payers, and society. A recent meta-analysis showed that early intervention for psychosis improved outcomes over time, including improved symptom severity and quality of life, reduced hospitalization, and better engagement with school and work.[7] Therefore, the value of the new indication in an adolescent population provides additional value to the product beyond the initial indications, which has not been appropriately recognized by ICER and integrated into its value analysis.

Recent studies have further demonstrated that REXULTI is a safe, effective, high-value treatment in the real-world.

Otsuka provided to ICER 14 additional scientific references to support the UPI review. These studies demonstrate that REXULTI improves clinical outcomes and patient quality of life, reduces medication discontinuation, reduces hospitalizations, emergency department (ED) visits and medical cost. The evidence package included 6 publications based on randomized clinical trials (RCT), a meta-analysis, 5 real-world evidence (RWE) studies, and 2 open-label studies, one based on a pharmacokinetic (PK) model. The studies represent just a sampling of the 144 publications and poster presentations identified in a targeted literature review of recent studies and analyses published between January 1, 2020 to March 31, 2022. These new clinical and research studies demonstrated that REXULTI improved clinical outcomes among patients with schizophrenia based on the PANSS scale,[1,8] and among patients with MDD, based on the Montgomery-

Asberg Depression Rating Scale (MADRS).[9] Another study also found that REXULTI corrected circadian dysfunction in patients with MDD and inadequate response to antidepressant treatment.[10]

New evidence also demonstrated that REXULTI improved patient quality of life and reduced risk of discontinuation, a major and costly challenge in treating those patients. Two studies also demonstrated that REXULTI resulted in improved life engagement,[11-12] while a third study demonstrated that REXULTI use in patients with MDD helped to reduce anxiety and lead to more calmness,[13] a clinical finding with important implications in managing this difficult to treat and expensive condition. A RWE analysis also showed that the risk of discontinuing treatment among patients with MDD, a major challenge in addressing this condition, was lower for REXULTI compared to other atypical antipsychotics.[14] In addition, a series of RWE studies have provided important evidence that use of REXULTI reduces health care resource utilization and medical costs relative to other atypical antipsychotics. For instance, unadjusted all-cause hospitalization (6.6% vs 12.5%) and ED visits (17.0% vs 27.5%) were lower with REXULTI compared to quetiapine extended release (XR) among patients with MDD. REXULTI-treated patients also had significantly lower mean medical costs ($6,421 vs $8,545, p=0.0123).[15] Another study showed that psychiatric costs in patients with MDD using lurasidone or quetiapine were $1,662 and $3,894 higher than patients using REXULTI.[16] Other studies consistently found that patients using REXULTI had lower psychiatric costs and reduced risk of psychiatric hospitalizations.[14, 17] These are substantial and important cost savings for both payers and society, which translate into clear and significant value.

Perhaps most importantly, recent studies have shown that REXULTI is a cost-effective therapy. A study presented at the 2022 Annual Psych Congress found that, among patients with MDD with inadequate response to antidepressant therapy (ADT), adjunctive REXULTI was cost-effective vs. quetiapine XR 150 mg/day, quetiapine XR 300 mg/day, olanzapine/fluoxetine 12/50 mg/day, and ADT alone, at a willingness to pay of $100,000.[18] This is substantial evidence and support of an economically justifiable price. Again, this is strong evidence of value and supports both a compelling clinical and cost-effectiveness rationale. ICER did not consider this piece of evidence when submitted. We urge ICER to modify the UPI assessment methodology to include more comprehensive value assessments, including cost-effectiveness modeling. Without doing so, ICER's conclusions are necessarily flawed and unreliable.

ICER's approach to drug pricing under UPI does not capture recent market conditions and does not accurately assess a drug's price or its value.

ICER estimates of price increases are methodologically flawed.

ICER stated that REXULTI took a 7.61% net price increase. However, the process by which ICER determined this net price increase is not transparent and is methodologically flawed. This assertion is incorrect. Because ICER's methodology is not transparent to us, we are not able to identify why and how the calculation fails to accurately reflect the product's net list price. ICER's statement that REXULTI's net price change resulted in $68 million in additional spending also is not accurate. The methodology relied on data from SSR Health, LLC. to estimate increase in net drug spending, but SSR Health's methodological approach suffers from measurement errors, given that, for some drugs identified through SSR Health's Rx Brand Pricing Data Tool, estimated net prices exceeded list prices.[19-20] We do not believe ICER should use an estimate that is derived from such a flawed methodology.

An alternative to consider would be taking a macroeconomic approach. Otsuka submitted an input-output price model that suggests a need to increase price of pharmaceuticals by 7.55% in response to changes in labor and capital costs of suppliers to pharmaceutical industry (Please refer to Otsuka's correspondence to ICER dated June 24, 2022 for the full model and report).

ICER's reliance on mCPI as price benchmark has significant limitations and is further evidence of a flawed methodology.

ICER's reliance on medical consumer price index (mCPI) as a benchmark for the UPI ignores important market dynamics. Criticisms of the use of mCPI are extensively discussed in Berndt et al. (2000).[21]

Moreover, mCPI has not risen at the same rate as CPI in the past few years due to societal forces such as the COVID pandemic[22] and the war in Ukraine.[23] Rather than focus on mCPI, drug prices should be assessed under a broader lens capturing market dynamics to reflect the realities of bringing drug products to the market during this rapidly inflationary period.

ICER's reliance on GRADE assessment is deeply flawed.

ICER's reliance on GRADE to make assessments for the UPI is deeply flawed, as there are severe limitations in these tools.[4] GRADE is subjective given the variability in the skills and training of raters creating significant low inter-rater reliability issues.[24] GRADE is also not appropriate to evaluate individual studies.

Further, GRADE is biased against observational studies.[24, 25] While RCTs have been considered the gold-standard for assessing safety and efficacy of a drug, the trial designs often have strict inclusion and exclusion criteria. As such, the evidence derived during RCTs may not always be generalizable or representative of what occurs in real world settings once a drug is on the market. Therefore, observational studies should also be considered to assess effectiveness of a product in the real world.[26] There is now growing evidence that the fidelity of results in an RCT can be reproduced in observational studies.[27-30] Furthermore, FDA[31] and the European Medicines Agency (EMA)[32] have issued guidance for inclusion of real-world evidence for regulatory decision-making.

ICER should focus on a comprehensive assessment of value, rather than price in isolation.

Otsuka submitted a catalog of evidence to support the clinical and economic value of REXULTI, including data from clinical trials, post-hoc analyses, RWE studies, and an updated cost-effectiveness analysis[18] based on a prior model for REXULTI.[33] However, ICER did not consider this evidence, but focused instead solely on the price increase in isolation. Otsuka recommends that ICER take into consideration a comprehensive view of value when assessing estimated price increases for products.

Closing Remarks

Otsuka is committed to serving those with unmet needs, especially in the important therapeutic areas of central nervous system (CNS) and nephrology. We have a long and proud history of serving individuals with severe mental illness and neurological conditions.

Accordingly, our launch of, and continued investment in, REXULTI is an important example of our philosophy to defy limitation so others can too. REXULTI is a clinically proven safe and effective high-value treatment that has been shown to improve patient clinical outcomes and quality of life while reducing medication discontinuation, hospitalizations, ED visits and hospital costs.

In addition to the approved indications of schizophrenia and major depressive disorder, Otsuka has implemented clinical trials of REXULTI for bipolar disorder, borderline personality disorder, agitation associated with Alzheimer's dementia, post-traumatic stress disorder, and irritability in autism.[34] Otsuka will continue this important work to improve the lives of people living with mental illness.

Our price for REXULTI is substantiated by the evidence provided, including new clinical evidence that led the FDA to approve an expanded indication into adolescent (aged 13-17) schizophrenia, an area of significant unmet medical need. In addition, the evidence demonstrated that REXULTI is a safe, effective, and cost-effective treatment for payers, patients, caregivers, providers, and society. Otsuka is proud of its commitment to mental health and will continue to innovate and deliver proven treatment options.

Sincerely,

Kaan Tunceli

Kaan Tunceli, PhD

Senior Director, Interim Head of Global Value & Real World Evidence

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Unsupported Price Increase Report
2022 Assessment

AbbVie Response to Lupron Assessment

October 26, 2022

AbbVie welcomes the opportunity to comment on ICER's Preliminary Unsupported Price Increase (UPI) assessments of Lupron. In this assessment, ICER aims to review new evidence to evaluate the increase in price from 2020 to 2021.

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. Further, AbbVie believes that ICER's UPI analysis is completely subjective and lacks scientific rigor. First, there are no industry standards, nor does ICER set any specific parameters in their methodology for exactly what new clinical evidence would support a price increase of a certain magnitude. Second, ICER utilizes an opaque, inconsistent, and incomplete process to determine whether sufficient clinical evidence exists to support price increases – a process that has varied widely every year of the report. Finally, ICER used IQVIA net price information to assess the net price impact of Lupron instead of using SSR Health as stated in their methodology. In fact, ICER did not mention any alternative sources of net price data could be used as part of their protocol.[1] Given this lack of scientific approach, one must conclude 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 the determination of value is informed by the totality of available clinical, economic, and humanistic evidence and utilizing a comprehensive approach to evidence, ranging from randomized studies, real-world evidence, and long-term follow-up studies to economic and humanistic evidence (i.e., health care resource utilization, work productivity, patient reported outcomes and patient preference). Value assessments, such as those put forth by ICER, provide an incomplete answer to whether a given treatment offers value.[2] In contrast, ICER does not perform full value assessments for the therapies selected for evaluation within its UPI report. Notably, ICER acknowledges this limitation within its UPI Protocol, admitting: *"…ICER does not 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."*[3] 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."*[4] 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, the UPI report is published every year. Further, ICER ignores 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 a UPI report based on the judgement of unnamed ICER reviewers determining whether they feel a price increase is supported based on their opinion of the new evidence available.

Of the evidentiary support provided by AbbVie, only one reference was determined by ICER to meet requirements for inclusion. Despite new evidence being available, ICER determined that Lupron did not have a price increase supported by clinical evidence. We question ICER's evaluation and interpretation of the submitted evidence for Lupron and bring to your attention the incomplete and misleading valuation caused by ICER's protocol methodology.

- ICER incorrectly states Lupron's indication in the treatment of advanced prostate cancer and fails to recognize an updated use for Lupron during the phase of this assessment.[5] As part of the evidentiary support for Lupron, AbbVie supplied ICER with the most current FDA approved label[6] for Lupron which indicates that Lupron is now approved for the treatment of advanced prostate cancer, not the *palliative* treatment of advanced prostate cancer stated in the ICER report. This change signifies the ability for all advanced prostate cancer patients to potentially benefit from Lupron, in addition to patients no longer undergoing active treatment. ICER has failed to review the most current FDA approved label, thereby ignoring an advance in how Lupron could be used to treat advanced prostate cancer.
- ICER rejected two of the submitted studies as "low quality". However, ICER does not provide rationale for why the studies were deemed "low quality".
    - Vargas et al[7] studied the impact of Lupron on height outcome in 48 patients with central precocious puberty (CPP) when treatment was initiated after chronological age (CA) of 7 years and continued beyond CA of 10 years or bone age (BA) of 12 years. The authors concluded that predicted adult height improved in most girls who initiated treatment after CA of 7 years. It continued to improve in most girls with longer treatment, even past BA of 12 years or CA of 10 years, which suggests that no absolute CA or BA limit should define initiation or end of treatment. Treatment plans need to be individualized, and neither treatment initiation nor cessation should be based on BA or CA alone. **Within this pediatric area, this study with 48 patients was anything but undersized - in fact, it was a majority subset (87%) of the trial population which was <u>accepted by the FDA</u> for the approval of Lupron in the treatment of central precocious puberty**. Moreover, this study was accepted and published by the peer-reviewed Journal of Pediatric Endocrinology & Metabolism, and thus offers objective scientific evidence for stakeholders. Yet, ICER rejected this study that a leading journal in the therapeutic area found scientifically credible, underscoring AbbVie's belief that ICER's UPI analysis is completely subjective and lacks scientific rigor.
    - Wallach et al[8] was a retrospective study evaluating whether real-world data can be used to emulate the results of randomized clinical trials. The study used electronic health record and administrative claims data to emulate the ongoing PRONOUNCE trial (A Trial Comparing Cardiovascular Safety of Degarelix Versus Leuprolide in Patients With Advanced Prostate Cancer and Cardiovascular

Disease). The study found that in 2,226 propensity score-matched patients with cardiovascular disease undergoing treatment for prostate cancer, degarelix was not associated with a lower risk of cardiovascular events than leuprolide. While this study was not a randomized clinical controlled trial, this study does represent the use of real-world evidence to understand the impacts of treatment, in alignment with the 21st Century Cures Act that among other intentions endorsed the importance of the use of real-world evidence. This study also aligns with the U.S. Food & Drug Administration and its published framework for its real-world evidence program that includes retrospective studies.[9]

It is also 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 on net price impact in their analysis. In ICER's published methodology for the UPI report, ICER states SSR Health net price data will be used to determine net price impact. However, in the analysis for Lupron, IQVIA data is used – a deviation from ICER's protocol and another example where this analysis does not follow scientific principles. This action again highlights the subjective nature of the UPI report.

As outlined above, AbbVie believes that the totality of evidence must be evaluated as part of any value measurement. 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 the concerns it has raised brings stakeholders 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 the concerns we raised about the methodology of ICER's UPI Assessment are important to consider and address to help ensure complete and reliable conclusions can be made by payers, policymakers, and patients to provide access to patients for the vital innovative therapies that they need and deserve.

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October 26, 2022

By Email: lcianciolo@icer.org

Laura Cianciolo
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RE: Ipsen response to ICER's preliminary Unsupported Price Increase (UPI) assessment of Somatuline® Depot (lanreotide) injection

Dear Laura:

Thank you for your reply of September 28, 2022. We appreciate the opportunity to comment on the ICER draft UPI assessment for SOMATULINE DEPOT.

SOMATULINE DEPOT is a critical therapy for thousands of Americans monthly.[1] Ipsen's modest price increases during your review period were both supported and merited. Ipsen strongly disagrees with ICER's inaccurate characterization of SOMATULINE DEPOT's price, and inclusion of SOMATULINE DEPOT on ICER's report.

In ICER's assessment, the Institute makes the assumption that patients would have a 20 percent coinsurance. However, most Medicare beneficiaries in traditional Medicare (83%) have supplemental coverage and have little to no cost sharing. [2]

During ICER's review, we raised three important reasons supporting SOMATULINE DEPOT's price increases during the period: 1) Increased Medicare Part B spend driven by an increase in the number of patients using SOMATULINE DEPOT, and not by drug price; 2) Medicare spend exacerbated by the suspension of sequestration; and 3) the cost of R&D innovation to benefit current and future patients. In summary:

- Increased Utilization: ICER's methodology for unsupported "price increase" measures Part B spend, not drug price. As the number of beneficiaries rises, so too does ICER's key evaluation metric. In this sense, ICER's assessment does not solely measure "price increase." In fact, demand for SOMATULINE DEPOT grew dramatically during the review period, with an additional 594 patients prescribed therapy in 2020. In total, $3.5M+ of the annual increase in Medicare Part B spend can be attributed to higher utilization

[1] Data on File. Projected based on Aug'22 IQVIA APLD and NSP data.
[2] A Snapshot of Sources of Coverage Among Medicare Beneficiaries in 2018 | KFF

driven by new SOMATULINE DEPOT patients and dose escalation, supported by the studies provided in Ipsen's June 24, 2022 response. ICER's report erroneously characterizes this growth in Medicare spend as increase in price.

- Suspension of Sequestration: The percent change in average Medicare spending per dosage unit 2019-2020 was exacerbated by the suspension of sequestration from May 1, 2020 through the rest of that year. When sequestration was suspended, the average spending per dosage unit in 2020 increased. In this respect, the Part B spending from 2019 to 2020 was artificially increased.

- Cost of Innovation: Despite its inclusion as allowable criteria, ICER did not consider the cost of innovation. Ipsen investment nearing $80M dollars for the current and next generation products demonstrates Ipsen's important critical commitment to discovering new uses of SOMATULINE DEPOT to help improve the lives of patients. Innovation is not free, and it is highly risky. Ipsen is proud of the investments it makes into research and development. Any objective review of "supported" price/cost increases should acknowledge this connection.

We also want to reiterate concerns regarding transparent calculation of "unit price increase." With an appreciation for the fact that Medicare Part B data exists within the confines of the CMS system, Ipsen respectfully objects to the sole reliance by ICER on CMS figures which are not independently verifiable. Please see section 3.2 "Definition and Calculation of "Unit Price Increase" from Ipsen's initial response for additional feedback.

In conclusion, we believe the combined effects of increased utilization, suspension of sequestration, the cost of R&D innovation, and ICER's inaccurate calculation of "price," justify the approximately 11.2% increase in per unit Part B spend ICER calculated.

If you have any questions, please contact me at (315) 439-2525 or at kimberly.baldwin@ipsen.com .

Sincerely,

Kimberly Baldwin

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October 26, 2022

RE: ICER's Unsupported Price Increase Assessment

Seagen is a global biotechnology company dedicated to revolutionizing cancer care. As a pioneer in novel therapies to treat cancer, our singular mission is to develop transformative medicines that make a meaningful difference in people's lives. To further Seagen's efforts, we are dedicated to enabling greater access to innovative medicines for the patients we serve by working with various stakeholders to support patients, including patient advocacy groups and physicians.

ADCETRIS is a groundbreaking medicine for the treatment of 2 rare types of lymphoma in 6 different indications and has been used to treat over 45,000 patients in the U.S. ADCETRIS is part of a broad clinical development program that includes over 60 company-sponsored completed or ongoing clinical trials and has been featured in more than 100 publications in high-quality, peer-reviewed journals. Seagen has invested, and continues to invest, in generating clinical and real-world evidence that demonstrates compelling benefit to people with cancer.

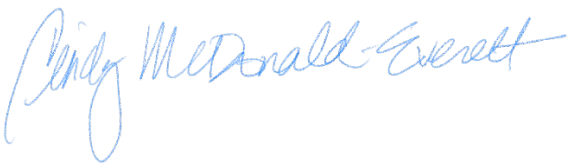
Seagen reiterates several concerns with the methodology that the Institute for Clinical and Economic Review (ICER) used in the selection and subsequent assessment of ADCETRIS in its report. Seagen's concerns with ICER's methodology include, but are not limited to, the limitations of Medicare data used in the analysis, the lack of transparency in assumptions related to patient cost burden, and most critically, the narrow, arbitrary, and unvalidated methodology employed to assess evidence. For example, ICER overlooked a key timeline of events related to the U.S. Food and Drug Administration (FDA) approval of ADCETRIS while rejecting key phase 3 data that demonstrated the value of the medicine. Specifically, ICER acknowledged that the ECHELON-2 study represented high-quality evidence that led to the FDA's November 16, 2018 approval of ADCETRIS for the treatment of CD30-positive peripheral T-cell lymphoma (PTCL). This approval was granted under the Real-Time Oncology Review (RTOR) Program and occurred less than 2 weeks after receipt of Seagen's

complete program application,[1] 20 weeks faster than the standard review timeline.[2] Following the FDA's accelerated approval, the ECHELON-2 results were presented at the American Society of Hematology (ASH) annual meeting on December 3, 2018 with a subsequent print publication of the full data in 2019 in Lancet,[3] a top-tier medical journal.

In its assessment, ICER rejected this publication, claiming it did not provide new information since FDA approval occurred in November 2018, and not within their January 2019-December 2020 window. ICER's assertion suggests that a standard, unaccelerated FDA review period would have met ICER's review timeframe for this assessment. It was precisely the compelling nature of this data – which ICER itself acknowledged as high-quality before ultimately disregarding it – that precipitated approval of ADCETRIS under this accelerated timeline.

Absent any significant rework of the ICER methodology that prevents high-quality, credible and timely evidence from being considered in its assessments, Seagen believes future ICER assessments will fail to meet stated objectives and not provide meaningful content to further dialogue on the value of innovative medicines in the U.S.

Sincerely,



Cindy McDonald Everett

Senior Vice President, Global Value Access

[1] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6516120/pdf/onco12917.pdf
[2] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review
[3] Horwitz S, O'Connor OA, Pro B, et al. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. Lancet. 2019;393(10168):229-40

Appendix

List of Select Publications

Abramson JS, Arnason JE, LaCasce AS, et al. Brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine for nonbulky limited-stage classical Hodgkin lymphoma. Blood. 2019;134(7):606-13.

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October 26th, 2022

RE: ICER UPI Medicare Part B Assessment of KRYSTEXXA® (pegloticase) injection

Horizon appreciates the opportunity to provide ICER with information supporting the enhanced value of KRYSTEXXA, per your request dated September 28, 2022. This document addresses the request from ICER for new evidence or analyses published or presented that demonstrate improved clinical or economic outcomes compared with what was previously believed for KRYSTEXXA (pegloticase injection).

Horizon is committed to developing therapies that can improve the lives of people living with rare diseases, and our recent research and development efforts for KRYSTEXXA epitomize this commitment. By limiting the presentation of data to 2019-2020, ICER's Unsupported Price Increase ("UPI") Medicare Part B assessment for KRYSTEXXA does not provide a complete view of the net health benefit of the use of methotrexate with KRYSTEXXA. Horizon's clinical research program studying the use of KRYSTEXXA with methotrexate began in 2019 and continued through 2022, ultimately demonstrating improved efficacy and safety that resulted in expansion of the FDA-approved label in July 2022 to include KRYSTEXXA co-administered with methotrexate. Yet, in its UPI Report, ICER declined to include any of the compelling data generated by Horizon over the last several years, and thus failed to capture the new clinical evidence supporting the benefit of KRYSTEXXA with methotrexate.

Note that KRYSTEXXA was included on the main list in the 2021 UPI report and is being included again in a new, alternative list related to Medicare Part B for the 2022 UPI report. The methodology of the new list brings KRYSTEXXA under evaluation for the exact same time period as the 2021 UPI report, using the exact same evidence submitted last year, however important additional evidence for healthcare providers and patients is available in the 2021-2022 time period, and KRYSTEXXA has since received an expansion of the FDA-approved label. Horizon presents the totality of evidence here as the clinical program for the use of methotrexate with KRYSTEXXA started in 2019 and continued through 2022. Limiting the presentation of data to the 2019-2020 time period does not provide a complete view of the net health benefit from the overall clinical program for the use of KRYSTEXXA with methotrexate.

In the UPI 2022 Protocol, ICER states that Additional Drugs to be Reviewed include therapies heavily covered under Medicare Part B that have the potential to present a financial burden on individual patients. In this discussion, however, ICER does not acknowledge the large percentage of Medicare Part B fee for service (FFS) patients with supplemental coverage and only states that patients who pay coinsurance face a large financial burden. Although studies have indicated that use of coinsurance in the *commercial* market may create a financial burden for patients, different dynamics exist under Medicare Part B.[i] Under Medicare Part B, the government pays 80% of the cost of Part B drugs while beneficiaries are responsible for the remaining 20%. An analysis from 2018 showed that 87% of patients that take Part B drugs have some form of supplemental coverage

for the 20% cost share, including Medigap (or Medicare Supplemental), employer sponsored coverage, Medicare Advantage or Medicaid. [ii] The share of beneficiaries with FFS coverage and Medicare Supplemental coverage increased from 35% to 39% from December 2017 to December 2020.[iii] According to America's Health Insurance Plans (AHIP), "only 4% of enrollees with Medicare Supplemental coverage reported having difficulty paying medical bills in the last 12 months."[iv] Horizon respectfully requests that ICER acknowledge the role supplemental coverage plays in affordability for beneficiaries with Medicare Part B FFS coverage when publishing the final report to provide a more holistic discussion of the stated purpose of the new list.

I. Horizon's Commitment to Patients with Rare Diseases

Since its inception in 2008, Horizon had one goal: bring breakthrough medicines – and hope – to people living with challenging diseases. Over a decade later, our focus remains on each patient whose life we can improve. Led by a CEO who lives with a rare disease and an autoimmune disease, our personal experiences fuel every decision we make; from the medicines we develop to the communities we support.

As a company, we are committed to addressing the long-term and systemic consequences of uncontrolled gout, actively advancing research for this often overlooked, stigmatized disease. This includes ongoing clinical research programs for KRYSTEXXA to improve the patient experience and outcomes. In addition, we have partnered with the scientific community and the patient community to develop a deeper understanding of the systemic impact of uncontrolled gout through both internal analyses and external sponsorship to examine the impact of uric acid on different areas of the body through real-world data and advanced imaging studies. These efforts aim to further our understanding of gout, current medications, and potential novel therapies that produce immediate and marked benefit for patient communities.

KRYSTEXXA was approved by the FDA as an orphan drug in 2010 for the treatment of chronic gout in adult patients refractory to conventional therapy[1], otherwise known as uncontrolled gout (estimated 1 – 3% of gout patients).[2] Uncontrolled gout occurs in patients who have failed to normalize serum uric acid (sUA) and whose signs and symptoms are inadequately controlled with xanthine oxidase inhibitors at the maximum medically appropriate dose or for whom these drugs are contraindicated. Patients with uncontrolled gout have long-standing disease with significant disease burden. The mean duration of gout in patients studied in the KRYSTEXXA registration trials was 15 years with a mean flare rate of 10 flares in the previous 18 months.[3] In addition, 56% of patients had evidence of gouty arthropathy and 71% had one or more visible (subcutaneous) tophi (urate crystal clusters on bones, in organs, and in soft tissues). An observational study of patients with uncontrolled gout who had a mean age of 59 years found that quality of life surrounding physical function (SF-36 [Short Form-36 questionnaire] physical function subscale) matched U.S. age and gender norms for people who were at least 16 years older.[4] In clinical studies, KRYSTEXXA markedly decreased tophus burden, which has been shown to provided clinical benefits including improvements in pain, physical function and health-related quality of life (Figure 1).[3,5-12] KRYSTEXXA is the only FDA-approved therapy for the treatment of uncontrolled gout. Our efforts to expand the efficacy and safety

profile of KRYSTEXXA through scientific data generation and better understand the impact of gout on patients exemplify our ongoing commitment to patients.

Figure 1: Effect of serum lowering with KRYSTEXXA on tophi[5]

II. ICER's Determination Does Not Reflect the Overall Clinical Value of New Evidence Supporting KRYSTEXXA

KRYSTEXXA often is used as the last line of treatment for patients with severe gout that cannot be controlled with oral urate-lowering gout therapies. Since acquiring KRYSTEXXA in 2016, Horizon has invested heavily in understanding and improving the safety and efficacy profile for KRYSTEXXA to address the unmet need in the uncontrolled gout patient population. The KRYSTEXXA Phase 3 registration trials demonstrated that 42% of patients on KRYSTEXXA had a sustained urate-lowering response through 6 months of treatment, leaving the majority of uncontrolled gout patients with no viable treatment options. As with other biologic medications, loss of treatment response was largely attributed to the development of anti-drug antibodies (ADAs). ADAs against KRYSTEXXA have also been associated with infusion reactions that occur during medication administration, which put patients at risk and lead to cessation of therapy.[2,3] ADAs are known to occur with biologic therapies and are associated with an increased risk of adverse reactions including infusion reactions and cessation of therapy.[14,15] As a last line therapy, KRYSTEXXA failure leaves a patient with no meaningful treatment options. Given that uncontrolled gout is associated with increased morbidity and mortality, disability, and high levels of pain, overall QOL is often severely impacted.

In an effort to improve both safety and efficacy, Horizon initiated a series of studies on the use of immunomodulators with KRYSTEXXA to prevent or minimize ADA development. Horizon's clinical research program for KRYSTEXXA with immunomodulation as co-therapy started in 2019, concluded in October 2021, and culminated in July 2022 with the expansion of the FDA-approved

label for KRYSTEXXA to include co-administered with methotrexate. Thus, the FDA's approval of KRYSTEXXA with methotrexate represented the culmination of years of effort and demonstrates Horizon's commitment to working together with the gout community to improve both patient experience and clinical outcomes.

The results from these studies were first made available in 2019 and 2020 and submitted to ICER as new evidence of clinical safety and effectiveness.[16-27] The evidence submitted on the use of immunomodulation (comprising methotrexate, mycophenolate mofetil, azathioprine and leflunomide; total of 72 patients) was compelling and suggested a response rate of 60% to 100% (an increase from 42% from the registration trials) with a reduction in the frequency of infusion reactions. Since 2020, a number of these studies have been published in peer-reviewed journals.[13,28-35] Data on immunomodulation with KRYSTEXXA led to increasing adoption of concomitant administration of KRYSTEXXA with immunomodulation by the clinical community in the treatment of patients with uncontrolled gout (from 1 – 4% in 2015 to 15% in 2019 and 16.8% in 2020).[25]

Based on the scientific evidence supporting the use of immunomodulation with KRYSTEXXA generated in 2019 and 2020, Horizon launched the MIRROR randomized controlled trial (RCT)—*Methotrexate to Increase Response Rates in Patients with Uncontrolled Gout receiving KRYSTEXXA*—results from which ultimately supported the label expansion for KRYSTEXXA. MIRROR RCT evaluated the safety and efficacy of oral methotrexate (MTX) as co-therapy with KRYSTEXXA in patients with chronic refractory or uncontrolled gout (N=152).[1,28] The primary endpoint (proportion of patients who achieved sUA <6 mg/dL for ≥80% of time during Weeks 20–24) was achieved in 71.0% of patients on KRYSTEXXA + MTX versus 38.5% of patients on KRYSTEXXA alone (p<0.0001). The incidence of new ADA formation was reduced with co-administration of methotrexate, resulting in higher KRYSTEXXA exposure and lower infusion reaction occurrence in patients co-treated with methotrexate (4.2% [includes 1 case of anaphylaxis based on NIAID/FAAN criteria]) than those receiving KRYSTEXXA alone (30.6%). The MIRROR RCT results thus reinforced the substantial body of data supporting the use of KRYSTEXXA with immunomodulation, which also includes the open-label studies discussed above and RECIPE (a Phase 2 randomized, double-blind, multicenter study evaluating the addition of mycophenolate mofetil to KRYSTEXXA)—all of which were submitted to ICER as new evidence.

The rationale behind ICER's decision to exclude 8 publications supporting use of immunomodulation with KRYSTEXXA from consideration in the UPI Report on the basis that they involve an "intervention/comparison not relevant to scope" or "outcomes not relevant to scope" is unclear and contradictory. As a threshold matter, it is difficult to understand how studies demonstrating improved efficacy and safety of KRYSTEXXA via concomitant use of an immunomodulatory agent would be considered outside the scope of an assessment intended to ascertain the value of KRYSTEXXA. These studies have already prompted a shift in the treatment paradigm for uncontrolled gout, confirming the value of this evidence to the medical community. Further confounding the assessment, ICER does not appear to apply a consistent methodology for determining which evidence is in- versus out-of-scope. Although ICER's assessment criteria provide

that ICER may exclude a given study for "multiple reasons," additional reasoning is not explained in the final report. For example, ICER apparently *did* accept one publication on the use of methotrexate with KRYSTEXXA as "in-scope," yet provided no rationale for excluding others that may have met the UPI criteria.

In addition to the clinical evidence supporting the use of immunomodulation with KRYSTEXXA, Horizon has prioritized research investigating comorbidities associated with gout. Hypertension, diabetes, chronic kidney disease and cardiovascular disease are commonly associated with gout, with a higher prevalence of these conditions in gout patients and an even higher prevalence in uncontrolled gout patients.[36-38] We are actively analyzing the KRYSTEXXA data to help clinicians understand the added benefits of KRYSTEXXA therapy among patients with comorbidities, including hypertension control, hepatic fibrosis and use in patients with renal disease.[8,39-42]

The profound impact of Horizon's clinical development program on people who have suffered for decades from the physical and emotional burden of uncontrolled gout should not be discounted. Uncontrolled gout patients have often endured a long clinical journey beset by diagnostic delays and under-treatment. Patients often have frequent painful acute gout attacks due to disease mismanagement and physician biases. ICER's exclusion of important data on immunomodulation perpetuates and exacerbates the neglect of this underserved patient population.

III. Conclusion

In conclusion, Horizon has substantially invested in research and development efforts to improve the safety and efficacy of KRYSTEXXA in patients afflicted with uncontrolled gout. We disagree with ICER's evaluation, which excludes from its review data beyond 2019-2020 and arbitrarily rejects clinically relevant evidence as outside the scope of the assessment, thus failing to provide a complete view of the net health benefit from the use of KRYSTEXXA with methotrexate. The recent FDA approval of an expanded label demonstrates the importance of these data. The robust KRYSTEXXA clinical trial program encompasses more than a decade of data, but the ICER UPI report captures only two-years of this longstanding and evolving clinical development program. Horizon believes its investment in clinical development supports the value and pricing of KRYSTEXXA. The FDA accepts this research as label-adjusting and has made methotrexate co-administration the new standard-of-care for KRYSTEXXA. To that end, we encourage ICER to ensure its UPI report criteria are applied in a manner that recognizes work published outside of the chosen review period and more comprehensively accounts for the merit of clinical research programs. Thank you for your consideration of this information.

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