



# Unsupported Price Increase Report

## Unsupported Price Increases Occurring in 2020

**December 16, 2021**

***Updated March 15, 2022***

Due to an email mix-up by ICER at the outset of this review, the manufacturer of Fanapt®, which was included solely based on policymaker recommendation, did not receive emails advising them of their opportunity to provide input and feedback to ICER.

After learning that the manufacturer did not receive the communications, ICER provided the company with the full timeframe for input and comment. This updated version of the 2020 report now includes the corrected assessment of Fanapt®.

**AUTHORS:** David M. Rind, MD, MSc  
Chief Medical Officer  
Institute for Clinical and Economic Review

Foluso Agboola, MBBS, MPH  
Vice President of Research  
Institute for Clinical and Economic Review

Dmitriy Nikitin, MSPH  
Research Lead, Evidence Synthesis  
Institute for Clinical and Economic Review

Avery McKenna  
Senior Research Assistant, Evidence Synthesis  
Institute for Clinical and Economic Review

Noemi Fluetsch, MSc, MPH  
Research Assistant, Health Economics and Outcomes Research  
Institute for Clinical and Economic Review

Jon Campbell, PhD, MS  
Senior Vice President for Health Economics  
Institute for Clinical and Economic Review

Francesca Beaudoin, MD, PhD, MS  
Senior Medical Advisor  
Institute for Clinical and Economic Review

Steven D. Pearson, MD, MSc  
President  
Institute for Clinical and Economic Review

**How to cite this document:** Rind DM, Agboola F, Nikitin D, McKenna A, Fluetsch N, Campbell J, Beaudoin F, Pearson SD. Unsupported Price Increase Report: Unsupported Price Increases Occurring in 2020. Institute for Clinical and Economic Review, December 6, 2021.  
<https://icer.org/assessment/unsupported-price-increase-2020/>.

**DATE OF PUBLICATION:** December 6, 2021

We would also like to thank Laura Cianciolo for her contributions to this report.

## About ICER

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

The funding for this report comes from government grants and non-profit foundations, with the largest single funder being the Arnold Ventures. No funding for this work comes from health insurers, pharmacy benefit managers, or life science companies. ICER receives approximately 29% of its overall revenue from these health industry organizations to run a separate Policy Summit program, with funding approximately equally split between insurers/PBMs and life science companies. Life science companies relevant to this review who participate in this program include AbbVie, Biogen, and Novartis. For a complete list of funders and for more information on ICER's support, please visit <https://icer.org/who-we-are/independent-funding/>.

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.

## Table of Contents

Executive Summary .....	ES1
1. Introduction .....	1
2. Selection of Drugs to Review .....	3
3. Assessments .....	8
3.1 Humira® (Adalimumab, AbbVie) .....	8
Introduction .....	8
Price Increase .....	8
Review of Clinical Evidence .....	8
Conclusion .....	10
3.2 Promacta® (Eltrombopag, Novartis) .....	11
Introduction .....	11
Price Increase .....	11
Review of Clinical Evidence .....	11
Conclusion .....	12
3.3 Tysabri® (Natalizumab, Biogen) .....	13
Introduction .....	13
Price Increase .....	13
Review of Clinical Evidence .....	13
Conclusion .....	14
3.4 Xifaxan® (Rifaximin, Bausch Health) .....	15
Introduction .....	15
Price Increase .....	15
Review of Clinical Evidence .....	15
Conclusion .....	16
3.5 Trokendi XR® (Topiramate, Supernus Pharmaceuticals) .....	17
Introduction .....	17
Price Increase .....	17
Review of Clinical Evidence .....	17
Conclusion .....	18

3.6 Venclexta® (Venetoclax, AbbVie) .....	19
Introduction .....	19
Price Increase .....	19
Review of Clinical Evidence .....	19
Conclusion .....	22
3.7 Lupron Depot® (Leuprolide Acetate, AbbVie).....	23
Introduction .....	23
Price Increase .....	23
Review of Clinical Evidence .....	23
Conclusion .....	24
3.8 Cimzia® (Certolizumab Pegol, UCB) .....	25
Introduction .....	25
Price Increase .....	25
Review of Clinical Evidence .....	25
Conclusion .....	27
3.9 Entresto® (Sacubitril/Valsartan, Novartis) .....	28
Introduction .....	28
Price Increase .....	28
Review of Clinical Evidence .....	28
Conclusion .....	31
3.10 Krystexxa® (Pegloticase, Horizon Therapeutics) .....	32
Introduction .....	32
Price Increase .....	32
Review of Clinical Evidence .....	32
Conclusion .....	33
3.11 Fanapt (Iloperidone, Vanda Pharmaceuticals).....	34
Introduction .....	34
Price Increase .....	34
Review of Clinical Evidence .....	34
Conclusion .....	34

3.12 Emflaza® (Deflazacort, PTC Therapeutics) .....	35
Introduction .....	35
Price Increase .....	35
Review of Clinical Evidence .....	35
Conclusion .....	36
References .....	37
Appendix A. Humira® .....	41
Appendix B. Promacta® .....	45
Appendix C. Tysabri® .....	46
Appendix D. Xifaxan® .....	49
Appendix E. Trokendi XR® .....	50
Appendix F. Venclexta® .....	51
Appendix G. Lupron Depot® .....	57
Appendix H. Cimzia® .....	59
Appendix I. Entresto® .....	63
Appendix J. Krystexxa® .....	64
Appendix K. Fanapt .....	66
Appendix L. Emflaza® .....	67
Appendix M. ICER Systematic Literature Review .....	68
Appendix N. ICER Responses to Manufacturer Comments .....	69
General Evidence Response .....	69
AbbVie .....	71
Bausch Health .....	72
Biogen .....	74
Horizon Therapeutics .....	75
Novartis .....	76
UCB .....	80

## List of Acronyms and Abbreviations Used in this Report

AWP	Average wholesale price
CI	Confidence interval
CPI	Consumer price index
E. coli	Escherichia coli
FDA	Food and Drug Administration
FSS	Federal Supply Schedule
HR	Hazard ratio
IBS-D	Irritable bowel syndrome with diarrhea
ICER	Institute for Clinical and Economic Review
NT-proBNP	N-terminal pro-B-type natriuretic peptide
OR	Odds ratio
RCT	Randomized controlled trial
TNF	Tumor necrosis factor
TPO-RA	Thrombopoietin receptor agonist
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.<sup>1-3</sup>

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 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 third 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 (2020) in the United States (US); this information came from SSR Health LLC, an independent investment research firm. We then excluded from this list 228 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 32 drugs, we estimated, where possible, the increase in spending in the US during 2019-2020 that was due to increases in net price as opposed to increases in volume. For the 14 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. Following our protocol, which allows for inclusion of up to three drugs based solely on public input that do not make the initial list, we added deflazacort (Emflaza®) and iloperidone (Fanapt®) for a total of 12 drugs for review.

Assessments were then performed on these 12 drugs to determine whether there was new clinical evidence in the prior two years (2019 through 2020) 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.<sup>4</sup> 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 for the 12 drugs included in this Report. Nine were judged to have price increases unsupported by new clinical evidence and three were found to have price increases with new clinical evidence. Net price increases for the drugs reviewed were mostly lower than in prior years of the UPI Report, and this is consistent with published data showing overall reductions in net prices in the US.<sup>5,6</sup> Although their significant revenue meant that even a small increase in net price would have a relatively large impact on national drug spending, two of the drugs reviewed, certolizumab pegol and sacubitril/valsartan, had net price increases below 1%.

The total increase in spending in the US over one year due to price increases for eight of the nine drugs found to have unsupported price increases amounted to \$1.67 billion; we do not have reliable estimates of change in spending due to price increases for deflazacort. This incremental budget impact of \$1.67 billion is larger than the \$1.2 billion from seven drugs with unsupported price increases seen in last year's UPI Report, but this is due, in greatest part, to the \$1.4 billion increase in spending due to unsupported net price increases for a single drug: adalimumab (Humira®).

As noted in a report from SSR Health LLC, national figures over the past several years suggest that overall net prices for drugs in the US market have decreased, and even list price increases have not exceeded the broader inflation in the economy.<sup>6</sup> Net pricing gains have been limited to drug categories in which product substitution is difficult or impossible (e.g., oncology, atypical anti-psychotics), and to certain situations, such as the imminent loss of exclusivity for adalimumab, when the anticipated drop in price leads payers to be less likely to switch patients to a competitor brand drug. Also of note in the current landscape is pending legislation in Congress that would set a cap on price increases for drugs in Medicare and the private market.<sup>7</sup> The changes in the market represent positive news for payers but have more mixed interpretation for patients, who continue, in many cases, to pay cost-sharing amounts linked to list prices. Depending on the outcome of federal legislation, the context for assessment of drug price increases may shift. Over the past year, however, some drugs have had unsupported price increases that have added significant costs to national drug spending, and as the market and policy landscape evolves, questions are likely to continue regarding the relationship of price increases to new information on clinical effectiveness.

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, even though three drugs did have new clinical evidence, this UPI Report does not attempt to determine whether the price increases were fully justified by meeting a health-benefit price benchmark that might be determined 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 we have taken an important first step in providing the public and policymakers with information they can use to advance the public debate on drug price increases.

**Table ES1. Drugs Selected for Assessment**

Drug (Generic)	2019 to 2020 Percentage Change*		Increase in Drug Spending Due to Net Price Change (in Millions)
	WAC	Net Price	
Drugs with Price Increases Unsupported by New Clinical Evidence			
Humira® (Adalimumab)	7.3%	9.6%	\$1,395
Promacta® (Eltrombopag)	7.2%	14.1%	\$100
Tysabri® (Natalizumab)	7.10%	4.20%	\$43.6
Xifaxan® (Rifaximin)	8.4%	3.0%	\$43.56
Trokendi XR® (Topiramate)	8.0%	12.4%	\$36
Lupron Depot® (Leuprorelin)	7.5%	5.9%	\$30
Krystexxa® (Pegloticase)	7.9%	5.2%	\$19
Fanapt® (Iloperidone)	10.8%	7.6%	\$6.2
Emflaza® (Deflazacort)	AWP (RED BOOK): 12.4%	VA FSS: -6.4%	N/A
Drugs with Price Increases with New Clinical Evidence†			
Venclexta® (Venetoclax)	7.6%	5.3%	\$34
Cimzia® (Certolizumab Pegol)	7.0%	0.9%	\$11.5
Entresto® (Sacubitril/Valsartan)	7.3%	0.7%	\$8

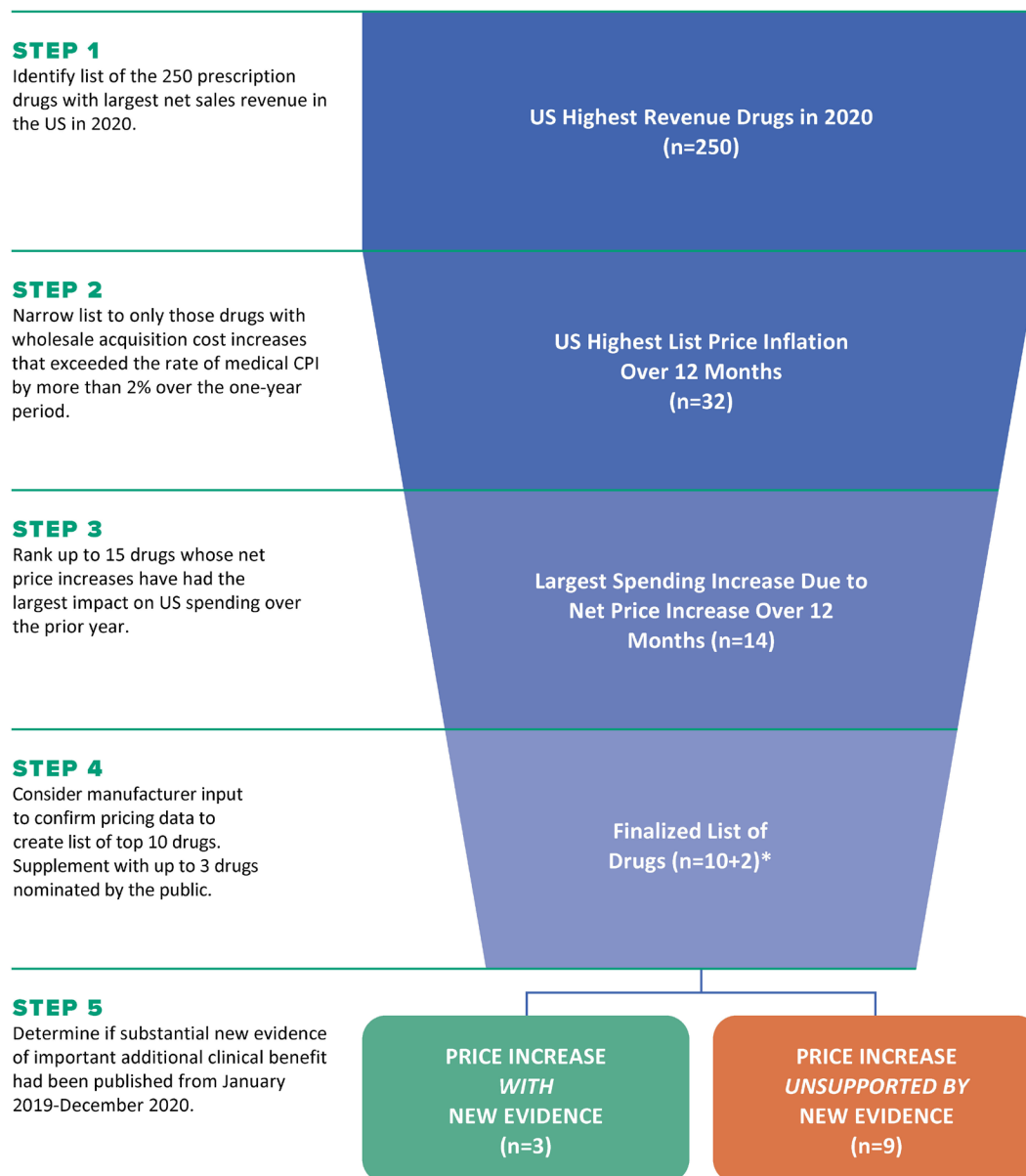
AWP: average wholesale price, N/A: not available, WAC: wholesale acquisition cost, VA FSS: Veterans Affairs Federal Supply Schedule

\*Year-over-year percentage changes were estimated by averaging over the four quarterly changes in price (i.e., Q1 2019 to Q1 2020; Q2 2019 to Q2 2020; Q3 2019 to Q3 2020 and; Q4 2019 to Q4 2020). Updates to AWP pricing reflect the same method as used for estimating average annual percentage changes in WAC and net price.

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

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.<sup>1-3</sup>

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 was comprised of representatives from patient groups, drugmakers, and insurers representing Medicaid and the private market. The first report looked back at two years of price increases and three years of new evidence.

ICER again worked with this group to develop a revised [UPI Protocol](#) for the reports. Important changes for this year's report include initially looking at the top 250 drugs (rather than top 100 drugs) by sales revenue so as to avoid missing large net price increases by drugs lower on the list, and changing to an inflation threshold of medical consumer price index (CPI) plus 2% rather than twice medical CPI given anticipated increases in baseline CPI.

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.

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.

Net price increases for the drugs reviewed were mostly lower than in prior years of the UPI Report, and this is consistent with published data showing overall reductions in net prices in the United States (US).<sup>5</sup> Two of the drugs reviewed had net price increases below 1%. ICER is encouraged to see this moderation of price increases and to be part of the milieu in which this moderation has occurred, but also notes that some drugs continued to have unsupported price increases with very

large impacts on US spending. Moving forward, ICER will work with the UPI advisory group to consider revising our methods in light of evolving market and policy landscapes.

## 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. Up to three additional drugs could be selected based on nominations received from the public. A detailed description of the entire [UPI Protocol](#) is available separately.

ICER obtained a list of the 250 drugs with the largest net sales revenue in the US in 2020. This information came from SSR Health, LLC, an independent investment research firm. For each drug, we then determined the average WAC price changes over a one-year period. For this UPI Report, we looked at the average price in 2020 compared with the average price in 2019.

**Table 2.1. List of Top 250 Drugs with the Highest Net Sales Revenue (in Millions) in the US in 2020**

Drug Name	Revenue†	Δ WAC‡	Drug Name	Revenue†	Δ WAC‡	Drug Name	Revenue†	Δ WAC‡
<b>Ranking†: 1-50</b>			Januvia®	\$1,470	4.9%	Lenvima®	\$771	5.6%
Humira®	\$16,112	7.3%	Hemlibra®	\$1,467	1.0%	Synthroid®	\$771	4.9%
Keytruda®	\$8,352	2.6%	Herceptin®	\$1,426	0.0%	Rebif®	\$756	7.5%
Revlimid®	\$8,291	5.9%	Xgeva®	\$1,405	2.9%	Symtuza®	\$738	4.4%
Biktarvy®	\$6,095	5.9%	Vraylar®	\$1,403	2.0%	Brilinta®	\$732	4.0%
Eliquis®	\$5,485	6.1%	Skyrizi®	\$1,385	7.6%	Pneumovax® 23	\$728	3.4%
Stelara®	\$5,240	4.7%	ProQuad®/M-M-R II/Varivax®	\$1,378	3.4%	Trelegy Ellipta®	\$725	5.0%
Eylea®	\$4,947	192.0%	Truvada®	\$1,376	5.8%	Cabometyx®	\$719	7.5%
Enbrel®	\$4,855	5.8%	Activase®/TNKase®	\$1,338	0.2%	Chantix®	\$717	5.6%
Imbruvica®	\$4,305	7.5%	Cimzia®	\$1,328	7.0%	Kyprolis®	\$710	4.7%
Opdivo®	\$3,945	2.3%	Sprycel®	\$1,295	6.0%	Fluarix®/FluLaval®	\$691	60.8%
Trulicity®	\$3,836	5.1%	Taltz®	\$1,289	6.0%	Takhzyro®	\$689	3.0%
Ibrance®	\$3,633	5.3%	Entresto®	\$1,277	7.3%	Mvasi®	\$656	0.0%
Ocrevus®	\$3,603	0.0%	Actemra®	\$1,277	4.4%	Rinvoq®	\$653	0.0%
Trikafta®	\$3,558	0.0%	Humalog®/Mix	\$1,267	0.0%	Afinitor®/Disperz®	\$644	0.3%
Dupixent®	\$3,174	3.0%	Alimta®	\$1,265	5.1%	Jynarque®	\$642	--
Rituxan®	\$3,016	0.0%	Vimpat®	\$1,210	3.2%	Premarin® Family	\$637	5.2%
Prevnar® Family	\$ 2,929	7.4%	Imfinzi®	\$1,184	3.0%	Austedo®	\$636	6.3%
Tecfidera®	\$2,678	5.9%	Odefsey®	\$1,172	6.0%	Tresiba®	\$633	0.1%
Genvoya®	\$2,605	5.9%	Simponi®/Aria	\$1,155	4.6%	Trintellix®	\$629	5.1%
Entyvio®	\$2,556	6.4%	Restasis®	\$1,150	5.0%	Aranesp®	\$629	0.0%
Ozempic®	\$2,525	4.9%	Tivicay®	\$1,125	5.0%	Adcetris®	\$626	8.1%
Cosentyx®	\$2,516	7.3%	Yervoy®	\$1,124	2.3%	Abilify Maintena®	\$620	1.2%
Remicade®	\$2,508	0.0%	Creon®	\$1,114	7.3%	Verzenio®	\$618	5.5%
Xarelto®	\$2,345	4.8%	Tysabri®	\$1,097	7.1%	Lexiscan®	\$614	0.0%
Invega Sustenna®/Trinza®	\$2,315	4.7%	Novolog®/Mix	\$1,094	0.0%	Vyndaqel®/Vyndamax®	\$613	0.3%
Orencia®	\$2,268	6.0%	Avonex®	\$1,084	2.0%	Breo Ellipta®	\$612	3.3%
Darzalex®	\$2,232	4.7%	Lantus®	\$1,049	0.1%	Vascepa®	\$598	9.0%
Xtandi®	\$2,170	3.3%	Opsumit®	\$1,008	4.7%	Parsabiv®	\$605	0.0%
Shingrix®	\$2,164	5.0%	Ingrezza®	\$993	3.5%	Fasenra®	\$603	3.0%
Vyvanse®	\$2,138	5.8%	Uptravi®	\$955	5.0%	Lupron®	\$600	7.5%
Pomalyst®	\$2,136	5.9%	Tremfya®	\$926	4.8%	Epogen®	\$598	0.0%
Veklury®	\$2,026	--	Velcade®	\$919	0.0%	Bridion®	\$584	5.0%
Xolair®	\$2,012	3.0%	Linzeß®	\$909	5.0%	Erleada®	\$583	4.7%
Neulasta®	\$2,001	0.0%	Lynparza®	\$875	2.0%	Advate®	\$577	3.3%
Jakafi®	\$1,938	3.9%	Abraxane®	\$873	4.9%	Acthar®	\$577	2.5%
Avastin®	\$1,891	0.0%	Humulin®/Mix	\$866	0.0%	Farxiga®/Xigduo®	\$569	4.0%
Triumeq®	\$1,879	5.0%	Tasigna®	\$859	7.5%	Tafinlar®/Mekinist®	\$569	5.6%
Latuda®	\$1,851	4.9%	Rexulti®	\$858	1.2%	Invokana®/Invokamet®	\$564	4.8%
Prolia®	\$1,830	4.7%	Kadcyla®	\$853	4.3%	Advair®	\$561	-0.2%
Fluzone®	\$1,821	-22.6%	Copaxone®	\$852	0.0%	<b>Ranking†: 151 - 200</b>		
Otezla®	\$1,790	5.4%	Bamlanivimab	\$850	--	Ninlaro®	\$546	2.1%
Gardasil®/9	\$1,754	3.3%	Prezista®/Prezcobix®	\$849	4.4%	Inlyta®	\$524	5.2%
Xyrem®	\$1,742	--	Basaglar®	\$842	0.0%	Gattex®	\$518	-72.7%
Victoza®	\$1,711	4.9%	Myrbetriq®	\$840	5.5%	Lo Loestrin® Fe	\$514	5.0%
Xeljanz®	\$1,706	5.3%	<b>Ranking†: 101-150</b>			Calquence®	\$511	0.0%
Botox®	\$1,664	0.0%	Sandostatin®/LAR	\$837	0.2%	Forteo®	\$510	5.1%
Tecentriq®	\$1,656	2.7%	Promacta®	\$833	7.2%	Eloctate®	\$502	2.9%
Aubagio®	\$1,632	5.0%	Esbriet®	\$832	4.5%	Juluca®	\$500	5.0%
Tagrisso®	\$1,566	2.0%	Symbicort®	\$831	4.0%	Orkambi®	\$497	0.0%
Gilenya®	\$1,562	5.6%	Tepezza®	\$820	--	Epclusa®	\$490	0.0%
<b>Ranking†: 51-100</b>			Venclexta®	\$804	7.6%			
Perjeta®	\$1,558	4.3%	Benlysta®	\$791	3.1%			
Jardiance®	\$1,533	6.0%	Spinraza®	\$788	2.0%			
Descovy®	\$1,526	5.9%	Mavyret®	\$785	0.0%			
Lucentis®	\$1,526	0.0%	Nucala®	\$772	3.2%			
Xifaxan®	\$1,482	8.4%						

Drug Name	Revenue†	Δ WAC‡
Saxenda	\$489	3.9%
Implanon/ Nexplanon	\$487	3.7%
Nplate	\$485	4.7%
RotaTeq	\$485	1.7%
Tyvaso®	\$483	4.2%
Erbix®	\$480	5.1%
Janumet®/XR	\$476	4.9%
Udenyca®	\$476	0.0%
Kanjinti®	\$475	0.0%
Levemir®	\$473	0.1%
Epidiolex®	\$468	6.0%
Novoseven®/RT	\$467	3.9%
Kalydeco®	\$461	0.0%
Pulmozyme®	\$461	0.0%
Repatha®	\$459	-45.6%
Zolgensma®	\$459	0.3%
Fabrazyme®	\$458	3.0%
Remodulin®	\$448	-0.9%
Menactra®	\$447	4.9%
Nuplazid®	\$442	12.1%
Inomax®	\$439	--
Norditropin®	\$432	6.8%
Anoro Ellipta®	\$423	3.0%
Injectafer®	\$419	6.6%
Exondys 51®	\$418	0.0%
Exparel®	\$413	4.1%
Krystexxa®	\$406	7.9%
Myozyme® /Lumizyme®	\$405	2.0%
Infanrix®/ Pediarix®	\$402	4.6%

Drug Name	Revenue†	Δ WAC‡
Ilaris®	\$400	2.0%
Bendeka®	\$388	0.0%
Bydureon®	\$383	4.0%
Cyramza®	\$382	5.1%
Aimovig®	\$378	4.7%
Zytiga®	\$373	0.1%
Alecensa®	\$363	4.5%
Yescarta®	\$362	--
Alprolix®	\$361	3.9%
Vemlidy®	\$356	5.9%
Northra®	\$356	8.1%
<b>Ranking†: 201-250</b>		
Dexilant®	\$350	3.1%
Lamictal®/XR	\$348	3.0%
Vectibix®	\$342	4.7%
Inflectra®	\$341	0.0%
Bexsero®	\$336	5.0%
Boostrix®	\$332	2.8%
Isentress®	\$326	7.5%
Emgality®	\$326	4.6%
Piqray®	\$320	5.8%
Trokendi XR®	\$320	8.0%
Kisqali®	\$318	5.6%
Suboxone® Film	\$317	4.9%
Xiaflex®	\$316	8.1%
Gleevec®	\$315	0.0%
Letairis®	\$314	5.9%
Symdeko®	\$314	0.0%
Gazyva®	\$310	2.3%
Multaq®	\$309	0.1%
Atripla®	\$307	5.8%
Bosulif®	\$305	5.3%

Drug Name	Revenue†	Δ WAC‡
Toujeo®	\$301	0.1%
Dovato®	\$296	5.3%
Risperdal Consta®	\$296	4.8%
Orenitram ER®	\$293	4.9%
Pentacel®	\$286	3.8%
Iclusig®	\$281	0.0%
Venofor®	\$279	-0.7%
Rybelsus®	\$278	5.9%
Jevtana®	\$278	5.1%
Procrit®	\$277	0.1%
Retacrit®	\$277	0.0%
Brovana®	\$276	4.2%
Engerix-B®	\$273	4.9%
Libtayo®	\$271	0.0%
Panznya®	\$270	0.1%
Zejula®	\$267	8.4%
Ravicti®	\$262	4.7%
Wellbutrin® XL	\$260	8.3%
Reblozyl®	\$259	--
Votrient®	\$259	5.8%
Lumigan®	\$254	5.0%
Tradjenta®	\$253	6.0%
Briviact®	\$248	3.0%
Adynovate®	\$242	3.1%
ProAir®	\$242	3.0%
Lonsurf®	\$241	5.1%
Adacel®	\$240	2.9%
BeneFIX®	\$239	2.9%
Flovent®	\$237	3.0%
Ocaliva®	\$234	4.8%

WAC: wholesale acquisition cost

\*No WAC change percentage is given when WAC data required to calculate WAC percentage change were not available in one or more quarters. Had the WAC percentage increases been larger than medical CPI + 2%, the drugs where WAC was unavailable still would not have been included in the list of drugs to be assessed.

†Net sales revenue in 2020, in millions.

‡Four quarter WAC change.

§Provided by manufacturer.

We then determined which of those drugs had a WAC price increase over the one-year period that exceeded the rate of medical CPI + 2%. This was calculated as the difference between the average medical CPI using unadjusted rates, which was 4.11% for 2020 relative to 2019. The medical CPI is one of eight major components of the CPI recorded and reported by the US Bureau of Labor Statistics.<sup>8</sup> Medical CPI comprises medical care services (professional services, hospital and related services, and health insurance) and medical care commodities (medical drugs, equipment, and supplies).<sup>9</sup> Drugs whose WAC price percentage increases had not exceeded the rate of medical CPI + 2% (6.11%) were removed from further evaluation. Our intent in choosing the overall medical CPI and not its subcomponents was to reflect inflation in drug prices relative to inflation in the overall price of medical care.

Among those 32 drugs with a WAC price increase greater than the medical CPI + 2%, we determined *net* price changes over the one-year period. WAC and net price change per unit over the one-year period were adjusted for percentage change in price across different dosing strengths for any drug,



if applicable, considering the relative sales volume of the various dosing strengths. Net price information was obtained from SSR Health. Drugs for which pricing information was deemed unreliable (e.g., because the net price was higher than WAC price in at least one of the eight quarters in which data were captured) were excluded from this review.

We then ranked those drugs whose net price increases had the largest impact on US spending over the prior year. To create this 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 2020, driven by both size of the product (in terms of total net sales) and size of the net price impact. Manufacturers were given the opportunity to correct these figures early in the process.

**Table 2.2. Drugs with WAC Percentage Change Greater Than Medical Care CPI\* + 2%**

Drug Name	Increase in Spending Due to Net Price Change (in Millions)	Drug Name	Increase in Spending Due to Net Price Change (in Millions)
Humira®	\$1,395	Creon®	-\$10
Promacta®	\$100	Entyvio®	-\$23
Tysabri®	\$43.6‡	Norditropin®	-\$206
Xifaxan®	\$43.56‡	Skyrizi®	\$
Trokendi XR®	\$36	Zejula®	\$
Venclexta®	\$34	Imbruvica®	\$
Lupron Depot®	\$30	Eylea®	\$
Krystexxa®	\$19	Prevnar® Family	\$
Cimzia®	\$11.5	Cabometyx®	\$
Entresto®	\$8‡	Fluarix®/FluLaval®	\$
Vascepa®	\$7.8‡	Austedo®	\$
Northera®	\$1	Adcetris®	\$
Cosentyx®	--†	Nuplazid®	\$
Rebif®	--†	Xiaflex®	\$
Injectafer®	-\$3	Tasigna®	--
Isentress®	-\$5	Wellbutrin XL®	--

CPI: consumer price index, WAC: wholesale acquisition cost

\*Medical care CPI was 4.11% in 2020.

†No positive net price increase per manufacturer.

‡Provided by manufacturer.

\$Because of lack of face validity, we do not show the change in drug spending for drugs that had a net price higher than WAC price in at least one of the eight quarters in which data were captured.

Table 2.2 shows the top 32 drugs listed by the effect of net price increases on US spending. The initial list included Cosentyx® and Rebif®, but the manufacturers provided corrected estimates that suggested no positive net price increase. Other corrections from manufacturers are also shown in the table. Manufacturers of the therapies with estimates that are shown as negative or that lacked face validity were not asked to review the results.

Table 2.3 shows the 12 drugs that were chosen for assessment. This includes the top 10 drugs from Table 2.2. The UPI process allows for up to three additional drugs to be reviewed based on public input. We received feedback asking ICER to review deflazacort (Emflaza®) and iloperidone (Fanapt®).

As no year-over-year WAC changes were readily available to us for deflazacort (Emflaza®), we estimated the year-over-year average wholesale price (AWP) change instead. Net price change was not available on SSR for this drug, and thus, we determined net price changes based on Veterans Affairs Federal Supply Schedule (VA FSS) pricing data. Pricing information for iloperidone (Fanapt®) was provided by the manufacturer.

**Table 2.3. Drugs Selected for Assessment**

Drug (Generic)	2019 to 2020 Percentage Change*		Increase in Drug Spending Due to Net Price Change (in Millions)
	WAC	Net Price	
Drugs with Price Increases Unsupported by New Clinical Evidence			
Humira® (Adalimumab)	7.3%	9.6%	\$1,395
Promacta® (Eltrombopag)	7.2%	14.1%	\$100
Tysabri® (Natalizumab)	7.1%	4.2%	\$43.6
Xifaxan® (Rifaximin)	8.4%	3.0%	\$43.56
Trokendi XR® (Topiramate)	8.0%	12.4%	\$36
Lupron Depot® (Leuprolerin)	7.5%	5.9%	\$30
Krystexxa® (Pegloticase)	7.9%	5.2%	\$19
Fanapt® (Iloperidone)	10.8%	7.6%	\$6.2
Emflaza® (Deflazacort)	AWP (REDBOOK): 12.4%	VA FSS: -6.4%	N/A
Drugs with Price Increases with New Clinical Evidence†			
Venclexta® (Venetoclax)	7.6%	5.3%	\$34
Cimzia® (Certolizumab Pegol)	7.0%	0.9%	\$11.5
Entresto® (Sacubitril/Valsartan)	7.3%	0.7%	\$8

AWP: average wholesale price, N/A: not available, WAC: wholesale acquisition cost, VA FSS: Veterans Affairs Federal Supply Schedule

\*Year-over-year percentage changes were estimated by averaging over the four quarterly changes in price (i.e., Q1 2019 to Q1 2020; Q2 2019 to Q2 2020; Q3 2019 to Q3 2020; and Q4 2019 to Q4 2020). Updates to AWP pricing reflect the same method as used for estimating average annual percentage changes in WAC and net price.

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

## 3. Assessments

---

### 3.1 Humira® (Adalimumab, AbbVie)

#### Introduction

Humira® (adalimumab, AbbVie) is a humanized monoclonal antibody that binds specifically to tumor necrosis factor (TNF).<sup>10</sup> It was approved by the Food and Drug Administration (FDA) in 2002, and is indicated for the treatment of nine different chronic diseases: rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, adult and pediatric Crohn's disease, adult and pediatric ulcerative colitis, plaque psoriasis, adult and adolescent hidradenitis suppurativa, and adult and pediatric noninfectious uveitis.<sup>10</sup>

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

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

#### Price Increase

Over the 12 months (four quarters) for which price changes were assessed, the WAC for adalimumab increased by approximately 7.3%, while its estimated net price increased by 9.6%. This net price change over the assessed four quarters resulted in an estimated increase in drug spending of \$1,395 million. All pricing information was obtained from SSR Health, LLC.

#### Review of Clinical Evidence

We reviewed the safety and clinical effectiveness information provided in the FDA label as well as related published literature to assess the baseline evidence on adalimumab as of January 2019. Following that, we conducted an independent systematic literature review, limited to RCTs, over the 24 months review timeframe (see [Tables M1-2](#) in Appendix M). In addition, we reviewed the RCT and non-RCT information AbbVie submitted to us to consider as new clinical information (54 references [26 conference presentations and 28 published manuscripts]). However, none of the identified or submitted articles met our criteria of new moderate to high-quality evidence on the benefits and/or harms of adalimumab within the indications that account for greater than 10% of use ([Table A1](#), Appendix A). Of the 54 references submitted by the manufacturer, seven articles

were duplicates, and 23 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 ([Appendix A](#) provides additional information on each study). Of the remaining 24 articles, 18 presented previously known information about adalimumab, while the remaining six studies were considered low quality. As an example, we highlighted one of the submitted articles (Chambers 2019) we classified as low-quality evidence.

**Table 3.1. Studies Not Meeting UPI Review Criteria\***

Reasons	Number of References
Study published outside of the timeframe of our review	3
Indication accounts for less than 10% of use	8
Intervention/comparison outside of our scope	5
Outcomes not relevant to our scope	7

\*Seven 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 3.2. Studies Not Meeting Criteria for New Moderate to High-Quality Evidence**

Reasons	Number of References
Low-quality evidence	6
Previously known information about adalimumab related to safety	1
Previously known information about adalimumab related to efficacy	17

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

**Chambers 2019** was a prospective controlled cohort study in 602 pregnant women that either received or did not receive adalimumab between 2004 and 2016.<sup>11</sup> A cohort of women with rheumatoid arthritis or Crohn's disease receiving at least one dose of adalimumab in the first trimester of pregnancy (adalimumab-exposed; n=257) was compared to a cohort of women with rheumatoid arthritis or Crohn's disease who did not receive adalimumab (disease-unexposed; n=120) and a cohort of healthy women who did not receive adalimumab (health-unexposed; n=225). Key outcomes, including major structural birth defects, preterm delivery, opportunistic infections, and malignancies, were collected through interviews, physical exams, and a review of medical records. The analysis showed that 10% of women in the adalimumab-exposed cohort had children born with a major birth defect compared to 7.5% in the diseased unexposed cohort (OR: 1.10, 95% CI: 0.45-2.73). No significant differences in serious or opportunistic infections were observed between the adalimumab-exposed cohort as compared to the disease unexposed cohort (95% CI: 0.34-2.77) or the healthy unexposed cohort (95% CI: 0.62-5.05). However, there was a higher rate of preterm birth in the adalimumab-exposed cohort compared to the healthy-unexposed cohort (HR: 2.59, 95% CI: 1.22-5.50), but not compared to the disease-unexposed cohort (HR: 0.82, 95% CI: 0.66-7.20).

***Reason(s) for Not Meeting Criteria for New Moderate to High-Quality Evidence:*** Chambers 2019 is a well-performed observational study conducted to address the safety of adalimumab in pregnancy. However, due to methodological limitations, including the small sample size of the registry, voluntary nature of participants, and short follow-up, this study does not reliably exclude a clinically important elevated risk of major birth defects with adalimumab. Therefore, using GRADE criteria, we conclude that we have low-quality evidence for assessing a change in conclusions about the net harms of adalimumab in pregnancy. Under the [UPI Protocol](#), we do not assess the magnitude of benefit in the absence of moderate or high-quality evidence.

## **Conclusion**

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

## 3.2 Promacta® (Eltrombopag, Novartis)

### Introduction

Promacta® (eltrombopag, Novartis) is a small molecule thrombopoietin receptor agonist that was approved by the FDA in 2008.<sup>12</sup> 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.<sup>12</sup> Eltrombopag is also approved for the treatment of severe aplastic anemia in patients who have had an insufficient response to immunosuppressive therapy.<sup>12</sup> Based on clinical input, both indications (thrombocytopenia and severe aplastic anemia) account for greater than 10% of eltrombopag's use.

### Price Increase

Over the 12 months (four quarters) for which price changes were assessed, the WAC for eltrombopag increased by approximately 7.2%, while its estimated net price increased by 14.1%. This net price change over the assessed four quarters resulted in an estimated increase in drug spending of \$100 million. All pricing information was obtained from SSR Health, LLC. The manufacturer suggested that net price changes were overestimated, but we did not receive corrected net price estimates from the manufacturer.

### Review of Clinical Evidence

We reviewed the safety and clinical effectiveness information provided in the FDA label as well as related published literature to assess the baseline evidence on eltrombopag as of January 2019. Following that, we conducted an independent systematic literature review, limited to RCTs, over the 24 months review timeframe (see [Tables M1-2](#) in Appendix M). In addition, we reviewed the RCT and non-RCT information Novartis submitted to us to consider as new clinical information (three references [one conference presentation 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 eltrombopag ([Table B1](#), Appendix B). Of the three references submitted by the manufacturer, one article was excluded because it did not meet our UPI review criteria, while the remaining two articles were considered low quality (see Tables 3.3 and 3.4). As an example, we highlighted the submitted article (Ruiz-Negron 2019) that did not meet the UPI criteria.

**Table 3.3. Studies Not Meeting UPI Review Criteria**

Reasons	Number of References
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 3.4. Studies Not Meeting Criteria for New Moderate to High-Quality Evidence**

Reasons	Number of References
Low-quality evidence	2

***Study Not Meeting UPI Review Criteria***

**Ruiz-Negron 2019** was a retrospective cohort study that utilized datasets from the US Veteran's Health Administration to compare long-term complication risks (i.e., cancer, infection, and any thromboembolic event) and mortality of thrombopoietin receptor agonists (TPO-RAs; eltrombopag and romiplostim) versus rituximab in veterans diagnosed with chronic immune thrombocytopenia after previous use of corticosteroids between 2011 and 2017.<sup>13</sup> Of the 31,501 veterans identified, 244 received a TPO-RA, while 185 received rituximab. There was no difference in risk of death between the two groups, but patients receiving TPO-RAs reported fewer long-term complications than those receiving rituximab (HR 0.73; 95% CI: 0.62-0.85).<sup>13</sup>

***Reason(s) for Not Meeting UPI Review Criteria:*** This study reports pooled data on TPO-RAs and does not provide information specifically on the effect of eltrombopag on long-term complications. As such, this study does not meet our UPI criteria for assessing new 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.

## 3.3 Tysabri® (Natalizumab, Biogen)

### Introduction

Tysabri® (natalizumab, Biogen) is an integrin receptor antagonist approved by the FDA in 2004.<sup>14</sup> It is indicated for the treatment of relapsing forms of multiple sclerosis and moderate-to-severe Crohn's disease in patients who have had an inadequate response to or are unable to tolerate conventional therapy and TNF inhibitors.<sup>14</sup> 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 natalizumab increased by approximately 7.1%, while its net price increased by 4.2%. This net price change over the assessed four quarters resulted in an increase in drug spending of \$43.6 million. The percent change for the net price and the associated increase in drug spending due to net price change was provided by the manufacturer whereas the percent WAC changes were estimated using SSR Health, LLC.

### Review of Clinical Evidence

We reviewed the safety and clinical effectiveness information provided in the FDA label as well as related published literature to assess the baseline evidence on natalizumab as of January 2019. Following that, we conducted an independent systematic literature review, limited to RCTs, over the 24 months review timeframe (see [Tables M1-2](#) in Appendix M). In addition, we reviewed the RCT and non-RCT information Biogen submitted to us to consider as new clinical information (35 references [11 conference presentations and 20 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 natalizumab ([Table C1](#), Appendix C). Of the 35 references submitted by the manufacturer, one article was a duplicate, and 14 articles were excluded because they did not meet our UPI review criteria. The primary reasons for excluding these studies are provided in Table 3.5 ([Appendix C](#) provides additional information on each study). Of the remaining 20 articles, 13 presented previously known information about natalizumab, while the remaining seven studies were considered low quality. As an example, we highlighted one of the submitted articles (Demortiere 2020) we classified as low-quality evidence.



**Table 3.5. Studies Not Meeting UPI Review Criteria\***

Reasons	Number of References
Study published outside of the timeframe of our review	11
Study population outside approved label indication	1
Intervention/comparison not relevant to scope	1
Outcomes not relevant to scope	1

\*One reference was identified as a duplicate submission 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 3.6. Studies Not Meeting Criteria for New Moderate to High-Quality Evidence**

Reasons	Number of References
Low-quality evidence	7
Previously known information about natalizumab related to safety	10
Previously known information about natalizumab related to efficacy	3

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

**Demortiere 2020** was a prospective observational study that evaluated the risks and benefits of stopping natalizumab treatment at conception or at the end of the first trimester in patients with highly-active relapsing-remitting multiple sclerosis planning pregnancy.<sup>15</sup> The study included 46 pregnancies (in 39 women), 30 for which treatment was continued through the first trimester per the clinic's standard, and 16 pregnancies where patients refused to continue natalizumab during pregnancies and instead stopped after conception. Results of the analysis showed a lower rate of relapse (3.6% vs. 38.5%,  $p < 0.005$ ) and disability progression (3.6% vs. 30.8%,  $p < 0.05$ ) during pregnancy in the secured first trimester group compared to the secured conception group. However, the two groups did not differ in terms of peripartum complications and fetal safety.

***Reason(s) for Not Meeting Criteria for New Moderate to High-Quality Evidence:*** Demortiere 2020 was conducted to address the benefit and risk of stopping natalizumab at conception versus continuing until the end of the first trimester. However, due to methodological limitations, including small sample size, allocation bias, lack of proper control, and potentially selective outcome reporting, this study does not reliably address the comparative benefits and risks of the two different treatment strategies. Therefore, using GRADE criteria, we conclude that this study provides low-quality evidence on the benefits and risks of stopping natalizumab at conception versus at the end of the first trimester. Under the [UPI Protocol](#), we do not assess the magnitude of benefit in the absence of moderate or high-quality evidence.

## **Conclusion**

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

## 3.4 Xifaxan® (Rifaximin, Bausch Health)

### Introduction

Xifaxan® (rifaximin, Bausch Health) is a rifamycin antibacterial drug originally approved by the FDA in 2004.<sup>16</sup> 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.<sup>16</sup>

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 8.4%, while its net price increased by 3.0%. This net price change over the assessed four quarters resulted in an increase in drug spending of \$43.56 million. The percent increase in net price and increase in drug spending were provided by the manufacturer, whereas the percent increase in WAC was obtained from SSR Health, LLC.

### Review of Clinical Evidence

We reviewed the safety and clinical effectiveness information provided in the FDA label as well as related published literature to assess the baseline evidence on rifaximin as of January 2019. Following that, we conducted an independent systematic literature review, limited to RCTs, over the 24 months review timeframe (see [Tables M1-2](#) in Appendix M). In addition, we reviewed the RCTs, and non-RCTs that Bausch Health submitted to us to consider as new clinical information (12 references [one conference presentation and 11 published manuscripts]). However, none of the identified or submitted articles met our criteria of new moderate to high-quality evidence on the benefits and/or harms of rifaximin within the indications that account for greater than 10% of use ([Table D1](#), Appendix D). Of the 12 references submitted by the manufacturer, two 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 ([Appendix D](#) provides additional information on each study). Of the remaining 10 articles, six presented previously known information about rifaximin, and the remaining four studies were considered low quality. As an example, we highlighted one of the submitted articles (Shah 2020) we classified as low-quality evidence.

**Table 3.7. Studies Not Meeting UPI Review Criteria**

Reasons	Number of References
Study published outside of the timeframe of our review	1
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**

Reasons	Number of References
Low-quality evidence	4
Previously known information about rifaximin related to efficacy	6

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

**Shah 2020** evaluated the cost effectiveness of treatments for IBS-D from three perspectives: insurer, societal, and patient.<sup>17</sup> The decision-analytic model was developed with a three-month cycle over a one-year time horizon. Patients were assumed to begin treatment immediately and entered one of two health states: “treatment response” or “no response.” Prescription drugs, including rifaximin, eluxadoline, and alosetron were more expensive than the alternative off-label drugs, dietary regimens, and cognitive behavioral therapy. The analyses showed that prescription drugs (rifaximin, eluxadoline, and alosetron) were dominated by alternative treatment options (cognitive behavioral therapy and dietary regimen) from both the insurer and societal perspective. However, the patient perspective highlights the out-of-pocket costs associated with these treatments. The out-of-pocket costs for the alternative treatments were relatively higher than that of alosetron and eluxadoline. However, the out-of-pocket cost for rifaximin was estimated to be similar or higher than the out-of-pocket cost for the alternative treatments and the other prescription drugs.

***Reason(s) for Not Meeting Criteria for New Moderate to High-Quality Evidence:*** This study highlights the differences in the insurer and patient perspectives when assessing the cost effectiveness of rifaximin and other treatments for IBS-D. However, using GRADE criteria, evidence from Shah 2020 is considered low quality in the absence of specific criteria that would increase the quality of evidence. In addition, this study does not provide any new information on a new net benefit on rifaximin (rifaximin was less cost effective than the other treatment options from both the insurer and patient perspectives).

## **Conclusion**

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

## 3.5 Trokendi XR® (Topiramate, Supernus Pharmaceuticals)

### Introduction

Trokendi XR® (topiramate, Supernus Pharmaceuticals), a carbonic anhydrase inhibitor, was originally approved by the FDA in 1996.<sup>18</sup> It is an extended-release formulation approved for epilepsy.<sup>18</sup> It is specifically used as monotherapy and adjunctive treatment in seizures classified as partial-onset or primary generalized tonic-clonic in patients ages six years and above as well as adjunctive therapy for seizures associated with Lennox-Gastaut syndrome in patients ages six years and above. In addition, topiramate is approved for preventive treatment of migraine in patients 12 years of age and older.<sup>18</sup> Based on the information provided by the manufacturer, 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 topiramate increased by approximately 8.0%, while its estimated net price increased by 12.4%. This net price change over the assessed four quarters resulted in an estimated increase in drug spending of \$36 million. All pricing information was obtained from SSR Health, LLC.

### Review of Clinical Evidence

We reviewed the safety and clinical effectiveness information provided in the FDA label as well as related published literature to assess the baseline evidence on topiramate as of January 2019. Following that, we conducted an independent systematic literature review, limited to RCTs, over the 24 months review timeframe (see [Tables M1-2](#) in Appendix M). Supernus Pharmaceuticals did not submit any references to be considered for our review. Our literature search identified five articles, of which two articles related to one RCT (FORWARD trial) met our inclusion criteria of new and potentially moderate to high-quality evidence on the benefits and/or harms of topiramate. Additional details on the FORWARD trial are provided below. The remaining three articles did not meet our UPI review criteria or presented previously known information about topiramate (Table 3.9).

**Table 3.9. Studies Not Meeting UPI Review Criteria**

Reasons	Number of References
Study population outside approved label indication	1
Study Protocol	1

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

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

Reasons	Number of References
Previously known information about topiramate related to efficacy	1

### ***New Evidence***

The **FORWARD study** was a randomized open-label prospective Phase IV study that evaluated the effectiveness of onabotulinumtoxinA (n=140) versus topiramate (n=142) in adult patients with chronic migraine.<sup>19</sup> Patients were randomized 1:1 to receive either onabotulinumtoxinA or topiramate for 36 weeks. A significantly higher proportion of patients randomized to onabotulinumtoxinA achieved the primary endpoint (a 50% or higher reduction in headache frequency at week 32) (40% vs. 12% in topiramate arm, adjusted OR, 4.9 [95% CI, 2.7-9.1]; p<0.001).<sup>19</sup> In addition, the patient-reported outcomes (Headache Impact Test; 9-Item Patient Health Questionnaire Quick Depression Assessment; Work Productivity Activity and Impairment Questionnaire; and Functional Impact of Migraine Questionnaire) favored onabotulinumtoxinA compared to topiramate.<sup>20</sup> Furthermore, there was a higher rate of adverse events (79% vs. 49%) and discontinuation (63% vs. 8%) in the topiramate arm than the onabotulinumtoxinA arm.<sup>19</sup>

### ***Rating of New Evidence (Quality and Magnitude)***

The FORWARD study presented new data on the effectiveness of onabotulinumtoxinA versus topiramate that favored onabotulinumtoxinA. The quality of the evidence is lowered by susceptibility to bias from its open-label design and by indirectness to the dosing/preparation of interest (the twice-daily topiramate [Topamax®] and not the once-daily extended-release topiramate [Trokendi XR®] was evaluated). We judge that using GRADE criteria, the FORWARD study provides moderate-quality evidence of an inferior net benefit of treatment with topiramate when compared with onabotulinumtoxinA in patients with chronic migraine.

### **Conclusion**

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

## 3.6 Venclexta® (Venetoclax, AbbVie)

### Introduction

Venclexta® (venetoclax, AbbVie) is a small-molecule inhibitor of B-cell lymphoma-2 approved by the FDA in 2016 for the treatment of adult patients with chronic lymphocytic leukemia or small lymphocytic lymphoma.<sup>21</sup> Venetoclax is also used in combination with azacitidine, decitabine, or low-dose cytarabine for the treatment of newly diagnosed acute myeloid leukemia in adults ages 75 years or older, who have comorbidities that preclude the use of intensive induction chemotherapy.<sup>21</sup>

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

- Chronic lymphocytic leukemia
- Acute myeloid leukemia.

### Price Increase

Over the 12 months (four quarters) for which price changes were assessed, the WAC for venetoclax increased by approximately 7.6%, while its estimated net price increased by 5.3%. This net price change over the assessed four quarters resulted in an estimated increase in drug spending of \$34 million. All pricing information was obtained from SSR Health, LLC.

### Review of Clinical Evidence

We reviewed the safety and clinical effectiveness information provided in the FDA label as well as related published literature to assess the baseline evidence on venetoclax as of January 2019. Following that, we conducted an independent systematic literature review, limited to RCTs, over the 24 months review timeframe (see [Tables M1-2](#) in Appendix M). In addition, we reviewed the RCT and non-RCT information AbbVie submitted to us to consider as new clinical information (70 references [54 conference presentations and 16 published manuscripts]). Of the 70 references submitted by the manufacturer, 31 articles were excluded because they did not meet our UPI review criteria. The primary reasons for excluding these studies are provided in Table 3.11 ([Appendix F](#) provides additional information on each study). Following our systematic literature review (see [Appendix F](#)) and the review of the remaining 39 articles submitted by the manufacturer, we identified seven references related to three RCTs (CLL4, VIALE-A, and VIALE-C) that met our criteria of new and potentially moderate to high-quality evidence on the benefits and/or harms of venetoclax. Additional details on these trials are provided below. The remaining 32 references submitted by the manufacturer presented previously known information about venetoclax or were considered low quality (Table 3.12).

**Table 3.11. Studies Not Meeting UPI Review Criteria**

Reasons	Number of References
Intervention/comparison not relevant to scope	9
Outcomes not relevant to our scope	15
Study population outside approved label indication	2
Study published outside of the timeframe of our review	5

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

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

Reasons	Number of References
Previously known information about venetoclax related to efficacy	17
Previously known information about venetoclax related to safety	1
Low-quality evidence	14

**Table 3.13. Summary of New Evidence**

Baseline Evidence (Before January 2019)	New Evidence
Based on data from the MURANO RCT and other single-arm trials, venetoclax was approved for adult patients with chronic lymphocytic leukemia who have received at least one treatment.	<p>The <b>CLL4</b> trial was an RCT that evaluated the efficacy and safety of venetoclax in patients with previously untreated chronic lymphocytic leukemia with coexisting medical conditions.<sup>22-24</sup></p> <p>Based on the evidence from the <b>CLL4</b> trial, the FDA expanded the approval for venetoclax to include adult patients with previously untreated chronic lymphocytic leukemia.</p>
Venetoclax received accelerated approval in combination with azacitidine, or decitabine, or low-dose cytarabine for the treatment of newly-diagnosed acute myeloid leukemia in adults who are age 75 years or older or who have comorbidities that preclude the use of intensive induction chemotherapy. Continued approval was contingent upon verification in confirmatory trials.	<p>Two RCTs (<b>VIALE-A</b> and <b>VIALE-C</b>) evaluated venetoclax in adult patients with newly-diagnosed acute myeloid leukemia who were 75 years or older or had comorbidities that made them ineligible for intensive induction chemotherapy.<sup>25-27</sup></p> <p>Based on the <b>VIALE-A</b> and <b>VIALE-C</b> trials, the FDA granted full approval for venetoclax in combination with azacitidine, or decitabine, or low-dose cytarabine for the treatment of newly diagnosed acute myeloid leukemia in adults 75 years or older or who have comorbidities that preclude the use of intensive induction chemotherapy.</p>

## **New Evidence**

The **CLL4 trial** was a Phase III open-label RCT that evaluated the efficacy and safety of venetoclax in patients with previously untreated chronic lymphocytic leukemia with coexisting medical conditions.<sup>25,27</sup> Patients were randomized 1:1 to receive either venetoclax combined with obinutuzumab (n=216) or chlorambucil plus obinutuzumab (n=216). The trial reported 30 primary events (disease progression or death) in the venetoclax plus obinutuzumab arm compared to 77 events in the chlorambucil plus obinutuzumab arm after a median follow-up of about 28 months (HR: 0.35; 95% CI: 0.23 to 0.53; p<0.001). In addition, based on the Kaplan-Meier estimate, the progression-free survival at 24 months was significantly higher in the venetoclax plus obinutuzumab arm (88.2%) compared to the chlorambucil plus obinutuzumab group (64.1%). Similarly, the other outcomes, including minimal residual disease negative rates (75.5% vs. 35.2%, p<0.001) and complete response rates (49.5% vs. 23.1%, p<0.001), favored the venetoclax group. At the time of data cutoff, median overall survival had not been reached in either group. Finally, similar rates of adverse events were observed in the two groups.

The **VIALE-A trial** was a Phase III multicenter RCT that evaluated the efficacy and safety of venetoclax in patients with confirmed acute myeloid leukemia who were ineligible for standard induction therapy because they were age 75 years or older or they had coexisting conditions or both.<sup>25</sup> Patients were randomized 2:1 to receive either venetoclax combined with azacitidine (n=286) or placebo plus azacitidine (n=145). At the time of the analysis, overall survival was significantly longer in the venetoclax group (14.7 months) compared to the placebo group (9.6 months) (HR for death: 0.66; 95% CI: 0.52 to 0.85; p<0.001). Similarly, the complete remission rate was higher in the venetoclax group (36.7% vs. 17.9%; p<0.001). However, key adverse events (e.g., nausea, neutropenia, febrile neutropenia, and infection) were more frequent in the venetoclax group compared to the control group.

The **VIALE-C trial** was a Phase III multicenter RCT that evaluated the efficacy and safety of venetoclax in patients with confirmed acute myeloid leukemia who were ineligible for standard induction therapy because they were ages 75 years or older or they had coexisting conditions or both.<sup>27</sup> Patients were randomized 2:1 to receive either venetoclax plus low-dose cytarabine (n=143) or placebo plus low-dose cytarabine (n=68). At the time of the analysis, although the overall survival was longer in the venetoclax group (7.2 months) compared to the placebo group (4.1 months), statistical significance was not reached (HR for death: 0.75; 95% CI: 0.52 to 1.07; p=0.11). However, the overall survival in the venetoclax arm achieved nominal significance after an additional six-month follow-up (HR: 0.70; 95% CI: 0.50-0.98; p=0.04). In addition, there was a higher rate of complete remission in the venetoclax group compared to the placebo group (27% vs. 7%; p<0.001). Key adverse events (e.g., nausea, neutropenia, febrile neutropenia, and infection) were higher in the venetoclax group compared to the placebo group.



### ***Rating of New Evidence (Quality and Magnitude)***

CLL4 provides new evidence on the use of venetoclax for adults with previously untreated chronic lymphocytic leukemia. The trial was open label and evaluated a surrogate outcome (progression free survival), providing moderate-quality evidence of a substantial benefit for the patient-important outcome of survival.

VIALE-A and VIALE-C examined an indication for which venetoclax previously had been granted accelerated approval. For this year's review, the [UPI Protocol](#) was amended to state:

*In the event that a drug was approved under the FDA Accelerated Approval pathway, ICER will consider new evidence that narrows uncertainty or confirms that a surrogate outcome predicted a patient-important outcome even if this evidence does not substantially alter prior beliefs.*

In combination, VIALE-A and VIALE-C provide high-quality evidence that venetoclax treatment for acute myeloid leukemia in older patients and those with comorbid conditions improves survival.

### **Conclusion**

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

## 3.7 Lupron Depot® (Leuprolide Acetate, AbbVie)

### Introduction

Lupron Depot® (leuprolide acetate, AbbVie) is a gonadotropin-releasing hormone agonist originally approved by the FDA in 1985.<sup>28</sup> It is indicated for the palliative treatment of advanced prostatic 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 of women with anemia caused by fibroids for whom three months of hormonal suppression is deemed necessary.<sup>28</sup> Leuprolide acetate is also approved for the treatment of pediatric patients with central precocious puberty.<sup>28</sup> Based on the information provided by the manufacturer, all the indications accounts 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 7.5%, while its estimated net price increased by 5.9%. This net price change over the assessed four quarters resulted in an estimated increase in drug spending of \$30 million. All pricing information was obtained from SSR Health, LLC.

### Review of Clinical Evidence

We reviewed the safety and clinical effectiveness information provided in the FDA label as well as related published literature to assess the baseline evidence on leuprolide acetate as of January 2019. Following that, we conducted an independent systematic literature review, limited to RCTs, over the 24 months review timeframe (see [Tables M1-2](#) in Appendix M). In addition, we reviewed the RCT and non-RCT information AbbVie submitted to us to consider as new clinical information (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 leuprolide acetate ([Table G1](#), Appendix G). Of the 16 references submitted by the manufacturer, 14 articles were excluded because they did not meet our UPI review criteria. The primary reasons for excluding these studies are provided in Table 3.14 ([Appendix G](#) provides additional information on each study). Of the remaining two articles, one presented previously known information about leuprolide acetate, while the remaining study was considered to be low-quality evidence. As an example, we highlighted one of the submitted articles (Armstrong 2019) that did not meet the UPI review criteria.

**Table 3.14. Studies Not Meeting UPI Review Criteria**

Reasons	Number of References
Intervention/comparison not relevant to our scope	9
Outcomes not relevant to our scope	1
Study published outside of the timeframe of our review	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 3.15. Studies Not Meeting Criteria for New Moderate to High-Quality Evidence**

Reasons	Number of References
Low-quality evidence	1
Previously known information about leuprolide acetate related to efficacy	1

### ***Study Not Meeting UPI Review Criteria***

**Armstrong 2019** was a Phase III multicenter RCT that evaluated the efficacy and safety of enzalutamide in patients with metastatic hormone-sensitive prostate cancer.<sup>29</sup> Patients were randomized 1:1 to receive either enzalutamide once daily (n=574) or placebo once daily (n=576); all patients continued to receive background androgen deprivation therapy. At the time of interim analysis, the median follow-up was 14.4 months. Enzalutamide plus androgen deprivation therapy demonstrated a statistically significant improvement in radiographic progression-free survival compared to placebo plus androgen deprivation therapy (enzalutamide median NR, placebo median: 19.0 months; HR: 0.39, 95% CI: 0.30-0.50). Interim analysis on overall survival showed that 6.8% of patients in the enzalutamide group had died compared to 7.8% in the placebo group (HR: 0.81; 95% CI, 0.53 to 1.25). The median overall survival was not reached in either group.

**Reason(s) for Not Meeting UPI Review Criteria:** Although leuprolide acetate is one of several gonadotropin-releasing hormone agonists used as androgen deprivation therapy for the treatment of prostate cancer, there is no evidence to show that leuprolide acetate was the background androgen deprivation therapy used in Armstrong 2019. And more importantly, Armstrong 2019 was designed to evaluate the efficacy of enzalutamide and not the background therapy. Thus, we excluded Armstrong 2019 because the evaluated intervention was not relevant to the scope of our review of leuprolide acetate.

## **Conclusion**

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

## 3.8 Cimzia® (Certolizumab Pegol, UCB)

### Introduction

Cimzia® (certolizumab pegol, UCB) is a TNF blocker.<sup>30</sup> It was approved by the FDA in 2008, and it is indicated for a variety of autoimmune and inflammatory conditions in adults, including Crohn's disease, rheumatoid arthritis (moderate-to-severe), psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis with objective signs of inflammation, and plaque psoriasis (moderate-to-severe).<sup>30</sup> Based on manufacturer input, our literature review, and clinical input, we are uncertain whether the indication of non-radiographic axial spondyloarthritis with objective signs of inflammation accounts for 10% of certolizumab pegol's use.

### Price Increase

Over the 12 months (four quarters) for which price changes were assessed, the WAC for certolizumab pegol increased by approximately 7.0%, while its net price increased by 0.9%. This net price change over the assessed four quarters resulted in an estimated increase in drug spending of \$11.5 million. The percent increase in net price was provided by the manufacturer whereas estimates for the percent increase in WAC and the increase in drug spending were obtained from SSR Health, LLC.

### Review of Clinical Evidence

We reviewed the safety and clinical effectiveness information provided in the FDA label as well as related published literature to assess the baseline evidence on certolizumab pegol as of January 2019. Following that, we conducted an independent systematic literature review, limited to RCTs, over the 24 months review timeframe (see [Tables M1-2](#) in Appendix M). In addition, we reviewed the RCT and non-RCT information UCB submitted to us to consider as new clinical information (49 references [30 conference presentations and 19 published manuscripts]). Of the 49 references submitted by the manufacturer, 10 articles were excluded because they did not meet our UPI review criteria. The primary reasons for excluding these studies are provided in Table 3.16 ([Appendix H](#) provides additional information on each study). Following our systematic literature review (see [Appendix H](#)) and the review of the remaining 39 articles submitted by the manufacturer, we identified six references<sup>31-36</sup> related to one RCT (C-axSpAnd trial) that met our criteria of new and potentially moderate to high-quality evidence on the benefits and/or harms of certolizumab pegol. Additional details on these trials are provided below. The remaining 32 references submitted by the manufacturer presented previously known information about certolizumab pegol or were considered low quality (Table 3.17).

**Table 3.16. Studies Not Meeting UPI Review Criteria\***

Reasons	Number of References
Intervention/comparison not relevant to scope	1
Outcomes not relevant to our scope	4
Study published outside of the timeframe of our review	5

\*One reference was identified as a duplicate submission 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 3.17. Studies Not Meeting Criteria for New Moderate to High-Quality Evidence**

Reasons	Number of References
Previously known information about certolizumab pegol related to efficacy	25
Previously known information about certolizumab pegol related to safety	3
Low-quality evidence	4

**Table 3.18. Summary of New Evidence**

Baseline Evidence (Before January 2019)	New Evidence
Certolizumab pegol was indicated for ankylosing spondylitis. At the time of the FDA review for the ankylosing spondylitis indication, UCB's originally proposed indication was for a broader indication of patients with active axial spondylarthritis. The FDA noted that the available data at that time did not support the approval of certolizumab pegol for patients with active axial spondylarthritis or patients with non-radiographic axial spondylarthritis. However, the submitted data was adequate to support the approval in ankylosing spondylitis. <sup>37</sup>	<p>The <b>C-axSpAnd</b> trial was an RCT that evaluated the efficacy and safety of certolizumab pegol in patients with patients with non-radiographic axial spondyloarthritis.<sup>31</sup></p> <p>Based on the data from the C-axSpAnd trial, the FDA granted approval for certolizumab pegol in patients with non-radiographic axial spondyloarthritis with objective signs of inflammation.</p>

### ***New Evidence***

The C-axSPAnd trial compared certolizumab pegol with placebo in 317 adult patients with non-radiographic spondyloarthritis. Patients were required to have active disease at baseline and the primary endpoint was the proportion of patients at one year achieving at least a 2-point decrease (labeled a major improvement) from baseline in the Ankylosing Spondylitis Disease Activity Score or achieving the lowest possible score of 0.6. More patients randomized to receive certolizumab pegol achieved this endpoint (47% vs. 7%;  $p < 0.0001$ ) despite 61% of placebo patients (and 13% of certolizumab pegol patients) switching to open-label treatment prior to one year.

### ***Rating of New Evidence (Quality and Magnitude)***

The C-axSPAnd Study provides high-quality evidence of a substantial benefit of treatment with certolizumab pegol for patients with non-radiographic spondyloarthritis. The prior action of the FDA to not approve this indication and the new FDA approval for this indication based on these results demonstrates that this is new information that was not generally accepted previously.

We are uncertain whether the indication of non-radiographic spondyloarthritis is responsible for at least 10% of the use of certolizumab pegol; our review suggests that it is likely in this range but could be lower than 10%. This indication is new as of 2019 and certolizumab pegol's use in non-radiographic spondyloarthritis is likely to be increasing over time. The [UPI Protocol](#) states:

*ICER will also seek manufacturer input on which indications result in approximately 10% or more of the overall utilization of that drug. If manufacturers report that an indication is currently below 10% of overall use but is rapidly increasing and evidence related to that indication is one justification for a price increase, ICER will consider reviewing evidence related to this indication.*

We believe that the information on use of certolizumab pegol allows evaluation of new evidence for the indication of non-radiographic spondyloarthritis.

## **Conclusion**

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

## 3.9 Entresto® (Sacubitril/Valsartan, Novartis)

### Introduction

Entresto® (sacubitril/valsartan, Novartis) is a twice-daily, single-tablet regimen that combines sacubitril (a neprilysin inhibitor) and valsartan (an angiotensin II receptor blocker).<sup>38</sup> It was approved by the FDA in 2015 and is indicated for reducing the risk of cardiovascular death and hospitalization in patients with chronic heart failure. The label notes that “*benefits of sacubitril/valsartan are most clearly evident in chronic heart failure patients with left ventricular ejection fraction below normal.*”<sup>38</sup> Sacubitril/valsartan is also approved for the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients (ages one year and older).<sup>38</sup> Based on the information provided by the manufacturer, only the first indication accounts for greater than 10% of use.

### Price Increase

Over the 12 months (four quarters) for which price changes were assessed, the WAC for sacubitril/valsartan increased by approximately 7.3%, while its net price increased by 0.7%. This net price change over the assessed four quarters resulted in an increase in drug spending of \$8 million. The percent increase in net price and increase in drug spending were provided by the manufacturer, whereas the percent increase in WAC was obtained from SSR Health, LLC.

### Review of Clinical Evidence

We reviewed the safety and clinical effectiveness information provided in the FDA label as well as related published literature to assess the baseline evidence on sacubitril/valsartan as of January 2019. Following that, we conducted an independent systematic literature review, limited to RCTs, over the 24 months review timeframe (see [Tables M1-2](#) in Appendix M). In addition, we reviewed the RCT and non-RCT information Novartis submitted to us to consider as new clinical information (21 references [one FDA advisory committee briefing document, two conference presentations, and 18 published manuscripts]). Of the 21 references submitted by the manufacturer, four articles were excluded because they did not meet our UPI review criteria. The primary reasons for excluding these studies are provided in Table 3.19 ([Appendix I](#) provides additional information on each study). Following our systematic literature review (see [Appendix I](#)) and the review of the remaining 17 articles submitted by the manufacturer, we identified six references<sup>39-44</sup> related to two RCTs (PIONEER-HF and PARAGON-HF) that met our criteria of new and potentially moderate to high-quality evidence on the benefits and/or harms of sacubitril/valsartan. Additional details on these trials are provided below. The remaining 11 references submitted by the manufacturer presented previously known information about sacubitril/valsartan or were considered low quality (Table 3.20).

**Table 3.19. Studies Not Meeting UPI Review Criteria**

Reasons	Number of References
Editorial	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 3.20. Studies Not Meeting Criteria for New Moderate to High-Quality Evidence**

Reasons	Number of References
Previously known information about sacubitril/valsartan related to efficacy	7
Low-quality evidence	3

**Table 3.21. Summary of New Evidence**

Baseline Evidence (Before January 2019)	New Evidence
<p><b>Sacubitril/valsartan was used to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (New York Heart Association Class II-IV) and reduced ejection fraction.<sup>38</sup></b></p> <p><b>This indication was largely based on the PARADIGM-HF trial, which enrolled outpatients with stable chronic heart failure. The trial excluded hospitalized patients with acute decompensated heart failure as well as new-onset heart failure patients.</b></p>	<p>The <b>PIONEER-HF</b> trial was an RCT that evaluated the efficacy and safety of sacubitril/valsartan in patients with new-onset or worsening chronic heart failure who were stabilized following hospitalization for acute decompensated heart failure.<sup>40</sup></p> <p>The PIONEER-HF trial extends the evidence base to populations that were excluded from previous trials – patients hospitalized for decompensated heart failure and patients with new heart failure.</p> <p>The <b>PARAGON-HF</b> trial was an RCT that evaluated the efficacy and safety of sacubitril/valsartan in patients with heart failure with preserved ejection fraction.<sup>39</sup></p> <p>Although <b>PARAGON-HF</b> did not reach its primary endpoint, in 2021, based on data from this trial, the FDA granted a label expansion for sacubitril/valsartan to include use in patients with heart failure with preserved ejection fraction. Specifically, the label was changed to say: “To reduce cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure. Benefits are most clearly evident in patients with left ventricular ejection fraction below normal.”<sup>38,45</sup></p>



## New Evidence

The **PIONEER-HF trial** was a randomized, active-controlled trial conducted in patients hospitalized with acute decompensated heart failure with reduced ejection fraction.<sup>40,42,43</sup> Patients were randomized 1:1 to receive either sacubitril/valsartan (n=440) or enalapril (n=441) twice daily with medication initiation occurring in the hospital. The time-averaged reduction in the N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration was significantly greater for sacubitril/valsartan versus enalapril at four weeks (percent change: -46.7% vs. -25.3%; ratio of change: 0.71; 95% CI: 0.63-0.81) with significantly greater reductions occurring as early as week one and lasting through week eight.<sup>40</sup> At week eight of follow-up, the sacubitril/valsartan arm had significantly lower rates of rehospitalization for heart failure compared to the enalapril arm (41 vs. 64 events; rate ratio: 0.64; 95% CI: 0.42-0.97) as well as lower rates of the composite outcome of cardiovascular death or rehospitalization for heart failure (9.8% vs. 16.3%; HR: 0.58, 95% CI: 0.40-0.85).<sup>40</sup> Rates of all-cause death were numerically lower in the sacubitril/valsartan arm (2.3% vs. 3.4%; HR 0.66, 95% CI: 0.30-1.48).<sup>40</sup> Results from a pre-specified analysis showed that patients with *de novo* heart failure had similar improvements in NT-proBNP concentration with sacubitril/valsartan versus enalapril (ratio of change: 0.65, 95% CI: 0.53-0.81) compared to patients with worsening chronic heart failure (ratio of change: 0.72, 95% CI: 0.63-0.83) at eight weeks.<sup>40</sup>

The **PARAGON-HF trial** was a randomized, active-controlled trial conducted in patients with symptomatic heart failure (New York Heart Association Class II to IV heart failure), left ventricular ejection fraction  $\geq 45\%$ , and structural heart disease.<sup>39,41,44</sup> Patients were randomized 1:1 to receive either sacubitril/valsartan (n=2,407) or valsartan (n=2,389).<sup>39</sup> The trial did not meet its primary endpoint of the composite of total (first and recurrent) hospitalizations for heart failure and death from cardiovascular causes (rate ratio: 0.87; 95% CI: 0.75 to 1.01; p=0.06). However, the incidence of hospitalization appears to be lower in the sacubitril/valsartan group (690 events vs. 797 events; rate ratio: 0.85; 95% CI: 0.72 to 1.00), while the incidence of death was similar in both groups (8.5% in the sacubitril/valsartan group vs. 8.9% in the valsartan group; HR: 0.95; 95% CI: 0.79 to 1.16). Results from the pre-specified subgroup analysis shows a heterogeneity of treatment effect by sex and left ventricular ejection fraction, suggesting that female patients and those with a left ventricular ejection fraction of 57% or lower may have a greater benefit with sacubitril/valsartan.<sup>39</sup>

## **Rating of New Evidence (Quality and Magnitude)**

ICER's [2020 UPI Report](#) stated:

*The PIONEER-HF trial represents high-quality evidence assessing the clinical benefit of sacubitril/valsartan in hospitalized patients with acute decompensated heart failure with reduced ejection fraction. Evidence from the PIONEER-HF trial indicates that sacubitril/valsartan reduced NT-proBNP concentration and the composite outcome of cardiovascular death or rehospitalization due to heart failure. This finding appears to be consistent irrespective of heart failure history (de novo vs. worsening or chronic heart failure). Although sacubitril/valsartan had previously demonstrated benefit in patients with stable heart failure with reduced ejection fraction, we believe there would have been potential concerns about its use in patients showing acute decompensation. As such, we believe that PIONEER-HF provides high-quality evidence of a substantial net benefit that was not previously known for patients with acute decompensated heart failure with reduced ejection fraction.*

We have no reason to alter this assessment of PIONEER-HF.

PARAGON-HF did not show a statistically significant reduction in its primary composite endpoint of hospitalization for heart failure or death from cardiovascular causes in patients with heart failure with preserved ejection fraction. In exploratory analyses conducted despite failure to achieve the primary endpoint, hospitalizations appeared to be modestly reduced (though with wide confidence intervals even not considering the uncertainties of the continued statistical analysis), and there appeared to be little effect on mortality. Using GRADE, the quality of the evidence is lowered for imprecision. We believe that PARAGON-HF provides moderate-quality evidence of an incremental benefit for patients with heart failure with preserved ejection fraction.

## **Conclusion**

The current ICER UPI Protocol did not anticipate the situation of an evaluated therapy having price increases two years in a row where new evidence could come from a single trial, however, that is the situation with sacubitril/valsartan. As such, and consistent with the [ICER 2020 UPI Report](#), we conclude that sacubitril/valsartan (Entresto®) had a price increase with new clinical evidence.

## 3.10 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.<sup>46</sup>

### Price Increase

Over the 12 months (four quarters) for which price changes were assessed, the WAC for pegloticase increased by approximately 7.9%, while its estimated net price increased by 5.2%. This net price change over the assessed four quarters resulted in an estimated increase in drug spending of \$19 million. All pricing information was obtained from SSR Health, LLC.

### Review of Clinical Evidence

We reviewed the safety and clinical effectiveness information provided in the FDA label as well as related published literature to assess the baseline evidence on pegloticase as of January 2019. Following that, we conducted an independent systematic literature review, limited to RCTs, over the 24 months review timeframe (see [Tables M1-2](#) in Appendix M). In addition, we reviewed the RCT and non-RCT information that Horizon Therapeutics submitted to us to consider as new clinical information (17 references [11 conference presentations and six 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 pegloticase ([Table J1](#), Appendix J). Of the 17 references submitted by the manufacturer, 15 articles were excluded because they did not meet our UPI review criteria. The primary reasons for excluding these studies are provided in Table 3.22 ([Appendix J](#) provides additional information on each study). Of the remaining two articles, one presented previously known information about pegloticase, and the remaining study was considered low-quality evidence. As an example, we highlighted one of the submitted articles (Edwards 2019) that did not meet the UPI review criteria.

**Table 3.22. Studies Not Meeting UPI Review Criteria**

Reasons	Number of References
Indication accounts for less than 10% of use	1
Study published outside of the timeframe of our review	1
Outcomes not relevant to our scope	6
Intervention/comparison not relevant to scope	6

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

**Table 3.23. Studies Not Meeting Criteria for New Moderate to High-Quality Evidence**

Reasons	Number of References
Low-quality evidence	2
Previously known information about pegloticase related to efficacy	1

### ***Study Not Meeting UPI Review Criteria***

Using data from two Phase III trials<sup>47,48</sup> conducted in chronic refractory gout patients, **Edwards 2019**<sup>49</sup> conducted a retrospective subgroup analysis of baseline characteristics and response to pegloticase treatment in patients with and without clinically apparent tophi. The analyses showed that, at baseline, patients with tophi had a longer disease duration, greater renal dysfunction, and more severe disease compared to those without tophi. However, the average number of acute flares in the 18 months prior to trial enrollment and serum urate levels were similar in the two groups. In addition, treatment with pegloticase resulted in clinical benefit in both groups of patients.

**Reason(s) for Not Meeting UPI Review Criteria:** Edwards 2019 was a retrospective study that attempted to characterize and compare patients with tophaceous versus non-tophaceous gout.<sup>49</sup> Although this study represents an important addition to the body of literature, the outcomes evaluated in this study are not relevant to our scope of evaluating new clinical information on the benefit of pegloticase.

## **Conclusion**

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

## 3.11 Fanapt® (Iloperidone, Vanda Pharmaceuticals)

### Introduction

Fanapt® (iloperidone, Vanda Pharmaceuticals) is an atypical antipsychotic agent approved by the FDA in 2009 for the treatment of schizophrenia in adult patients.<sup>1</sup>

### Price Increase

Iloperidone was added to this review based on stakeholder input. Over the 12 months (four quarters) for which price changes were assessed, the WAC for iloperidone increased by approximately 10.8%, while its estimated net price increased by 7.6%. This net price change over the assessed four quarters resulted in an estimated increase in drug spending of \$6.2 million. All pricing information was submitted by the manufacturer.

### Review of Clinical Evidence

We reviewed the safety and clinical effectiveness information provided in the FDA label as well as related published literature to assess the baseline evidence on iloperidone as of January 2019. Following that, we conducted an independent systematic literature review, limited to RCTs, over the 24 months review timeframe. However, this review did not yield any relevant results. Additionally, Vanda Pharmaceuticals did not submit any references for us to consider as new clinical information.

### Conclusion

We did not identify or receive any new evidence on iloperidone. Thus, we conclude that iloperidone (Fanapt) had a price increase unsupported by new clinical evidence.

## 3.12 Emflaza® (Deflazacort, PTC Therapeutics)

### Introduction

Emflaza® (deflazacort, PTC Therapeutics) is a corticosteroid approved by the FDA in 2017 for the treatment of Duchenne muscular dystrophy in patients two years of age and older.<sup>50</sup>

### Price Increase

Deflazacort was added to this review based on stakeholder input. Over the 12 months (four quarters) for which price changes were assessed, the average wholesale price for deflazacort increased by approximately 19.0% based on REDBOOK, while the Federal Supply Schedule annual change in price decreased by 6.4% (from 2019 to 2020). We were not able to estimate generalizable annual net price changes. The estimated increase in drug spending due to net price changes over the assessed four quarters was not available. The manufacturer reported net product revenue in 2020 of \$139 million, which translates to a 38% increase compared to 2019.<sup>51</sup> It is unknown whether this increase in revenue was due to net price changes. Pricing information for deflazacort was not available from SSR Health, LLC.

### Review of Clinical Evidence

We reviewed the safety and clinical effectiveness information provided in the FDA label as well as related published literature to assess the baseline evidence on deflazacort as of January 2019. Following that, we conducted an independent systematic literature review, limited to RCTs, over the 24 months review timeframe (see [Tables M1-2](#) in Appendix M). In addition, we reviewed the RCT and non-RCT information PTC Therapeutics submitted to us to consider as new clinical information (four references [one conference presentation and three 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 deflazacort ([Table L1](#), Appendix L). Of the four references submitted by the manufacturer, two articles were excluded because they did not meet our UPI review criteria. The primary reasons for excluding these studies are provided in Table 3.24 ([Appendix L](#) provides additional information on each study). Of the remaining two articles, both presented previously known efficacy information about deflazacort. As an example, we highlighted one of the submitted articles (McDonald 2020) that presented previously known information about deflazacort.

**Table 3.24. Studies Not Meeting UPI Review Criteria**

Reasons	Number of References
Study published outside of the timeframe of our review	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 3.25. Studies Not Meeting Criteria for New Moderate to High-Quality Evidence**

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

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

**McDonald 2020**<sup>52</sup> is a meta-analysis of observational data nested in the placebo arms of two RCTs designed to evaluate ataluren (ACT DMD trial)<sup>53</sup> and tadalafil (Victor 2017)<sup>54</sup> in ambulatory male patients ages seven to 14 years with Duchenne muscular dystrophy. The meta-analysis evaluated and compared the efficacy data for the patients who were randomized to the placebo arm of the ACT DMD and Victor 2017 trials and received either deflazacort or prednisone. The results of the analyses generally favored deflazacort treatment, showing a lower rate of decline in function as measured by six-minute walk distance (28.3 meters; 95% CI: 5.7 to 50.9 meters), time to rise from supine (2.9 seconds; 95% CI: 0.9 to 4.9), time of four-stair climb (2.3 seconds; 95% CI: 0.5 to 4.1). However, no difference was seen between the two drugs on the 10-meter walk/run and North Star Ambulatory Assessment score.

**Reason(s) for Not Meeting Criteria for New Moderate to High-Quality Evidence:** The findings in this meta-analysis are consistent with what has been shown in previous studies<sup>53-55</sup> and evaluations<sup>56</sup> of deflazacort. Deflazacort may provide greater benefits on motor function compared to prednisone. However, not all data are consistent, and the size of the benefits may be small. Thus, we deemed this reference to contain previously known information about deflazacort related to efficacy.

## **Conclusion**

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

# References

---

1. Horvath J. Update: What's New in State Drug Pricing Legislation? <https://nashp.org/update-whats-new-in-state-drug-pricing-legislation/>. Published 2018. Accessed 10/04/19, 2019.
2. An act relating to prescription drugs [press release]. 2016.
3. Health care: prescription drug costs. In: Hernandez, ed. *Health and Safety Code, Insurance Code*. Vol 2017-2018.
4. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ (Clinical research ed)*. 2008;336(7650):924-926.
5. Silverman E. Inflation and rebates caused wholesale prices on medicines to drop in second quarter. <https://www.statnews.com/pharmalot/2021/09/27/inflation-drug-prices-rebates-insulin-diabetes-cancer/>. Published 2021. Accessed October 19, 2021.
6. SSR Health. *2Q21 List and net price trends for US Rx brands*. September 21, 2021.
7. O'Brien S. Latest version of Democrats' \$1.75 trillion budget bill includes improvements to Medicare's coverage. *Personal Finance*. 2021. <https://www.cnn.com/2021/11/03/latest-version-of-democrats-budget-bill-includes-medicare-changes.html>. Published 11/3/21. Accessed 11/11/21.
8. Labor USDo. Bureau of Labor Statistics. <https://www.bls.gov/home.htm>. Published 2020. Accessed 12/22/20.
9. Labor USDo. Measuring Price Change in the CPI: Medical care. 2020.
10. Food and Drug Administration. Humira (adalimumab) Package Insert - February 2021. 2021.
11. Chambers CD, Johnson DL, Xu R, et al. Birth outcomes in women who have taken adalimumab in pregnancy: A prospective cohort study. *PloS one*. 2019;14(10):e0223603.
12. Food and Drug Administration. Promacta (eltrombopag) Package Insert - February 2021. 2021.
13. Ruiz-Negron N, Crook J, Rondina MT, et al. Comparing the Risk of Complications for Second-Line Treatments of Immune Thrombocytopenia in Veterans: A US National Study. *Blood*. 2019.
14. Food and Drug Administration. Tysabri (natalizumab) Package Insert - June 2020. 2020.
15. Demortiere S, Rico A, Maarouf A, Boutiere C, Pelletier J, Audoin B. Maintenance of natalizumab during the first trimester of pregnancy in active multiple sclerosis. *Multiple Sclerosis Journal*. 2021;27(5):712-718.
16. Food and Drug Administration. Xifaxan (rifaximin) Package Insert - November 2020. 2020.
17. Shah ED, Salwen-Deremer JK, Gibson PR, Muir JG, Eswaran S, Chey WD. Comparing costs and outcomes of treatments for irritable bowel syndrome with diarrhea: cost-benefit analysis. *Clinical Gastroenterology and Hepatology*. 2020.
18. Food and Drug Administration. TROKENDI XR (topiramate) Package Insert - November 2020. In:2020.
19. Rothrock JF, Adams AM, Lipton RB, et al. FORWARD study: evaluating the comparative effectiveness of onabotulinumtoxinA and topiramate for headache prevention in adults with chronic migraine. *Headache: The Journal of Head and Face Pain*. 2019;59(10):1700-1713.
20. Blumenfeld AM, Patel AT, Turner IM, Mullin KB, Manack Adams A, Rothrock JF. Patient-reported outcomes from a 1-year, real-world, head-to-head comparison of onabotulinumtoxinA and topiramate for headache prevention in adults with chronic migraine. *Journal of Primary Care & Community Health*. 2020;11:2150132720959936.
21. Food and Drug Administration. Venclexta (venetoclax) Package Insert - November 2020. 2020.



22. Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and Obinutuzumab in Patients with CLL and Coexisting Conditions. *New England Journal of Medicine*. 2019;380(23):2225-2236.
23. Fischer K, Al-Sawaf O, Bahlo J, Fink A, Tandon M, al. e. Effect of fixed-duration venetoclax plus obinutuzumab (VenG) on progression-free survival (PFS), and rates and duration of minimal residual disease negativity (MRD-) in previously untreated patients (pts) with chronic lymphocytic leukemia (CLL) and comorbidities. *Journal of Clinical Oncology*. 2019;37(15\_suppl):7502-7502.
24. Al-Sawaf O, Fink A-M, Robrecht S, et al. Prevention and Management of Tumor Lysis Syndrome in Patients with CLL and Coexisting Conditions Treated with Venetoclax-Obinutuzumab or Chlorambucil-Obinutuzumab: Results from the Randomized CLL14 Trial. *Blood*. 2019;134(Supplement\_1):4315-4315.
25. DiNardo C, Jonas B, Pullarkat V, et al. A Randomized, Double-Blind, Placebo-Controlled Study of Venetoclax with Azacitidine vs. Azacitidine in Treatment-Naive Patients with Acute Myeloid Leukemia Ineligible for Intensive Therapy - VIALE-A. European Hematology Association (EHA) 25th Annual Meeting; 2020; Virtual.
26. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. *New England Journal of Medicine*. 2020;383(7):617-629.
27. Wei AH, Montesinos P, Ivanov V, et al. Venetoclax plus LDAC for newly diagnosed AML ineligible for intensive chemotherapy: a phase 3 randomized placebo-controlled trial. *Blood*. 2020;135(24):2137-2145.
28. Food and Drug Administration. LUPRON DEPOT (leuprolide acetate) Package Insert - March 2021. 2021.
29. Armstrong AJ, Szmulewitz RZ, Petrylak DP, et al. ARCHES: a randomized, phase III study of androgen deprivation therapy with enzalutamide or placebo in men with metastatic hormone-sensitive prostate cancer. *Journal of Clinical Oncology*. 2019;37(32):2974.
30. Food and Drug Administration. Cimzia (certolizumab pegol) Package Insert - September 2019. 2019.
31. Deodhar A, Gensler LS, Kay J, et al. A fifty - two-week, randomized, placebo - controlled trial of certolizumab pegol in nonradiographic axial spondyloarthritis. *Arthritis & Rheumatology*. 2019;71(7):1101-1111.
32. Deodhar A GL, Kay J, Maksymowych WP, Haroon N, Landewe R, Rudwaleit M, Hall S, Wei J, Bauer L, Hoepken B, De Peyrecave N, Kumke T, Van Der Heijde D Certolizumab pegol versus standard care in treating non-radiographic axial spondyloarthritis: results for Asia-Pacific versus rest of the world from C-axSpAnd. *International journal of rheumatic diseases*. 2019;22:83.
33. Deodhar A, Gensler L, Kay J, et al. Certolizumab Pegol Improves Work and Household Productivity and Social Participation over 1 Year of Treatment in Patients with Non-Radiographic Axial Spondyloarthritis. Paper presented at: ARTHRITIS & RHEUMATOLOGY2019.
34. Gensler L, Kay J, Maksymowych WP, et al. Certolizumab Pegol-Treated Patients with Non-Radiographic Axial Spondyloarthritis Demonstrate Improvements in Sleep Quality and Other Patient Reported Outcomes. Paper presented at: ARTHRITIS & RHEUMATOLOGY2019.
35. Deodhar A, Gensler L, Hall S, et al. Certolizumab Pegol Efficacy in Patients with Non-Radiographic Axial Spondyloarthritis Stratified by Baseline MRI and C-Reactive Protein Status. Paper presented at: ARTHRITIS & RHEUMATOLOGY2020.
36. Kay J, Gensler L, Deodhar A, et al. Earlier Treatment of Non-Radiographic Axial Spondyloarthritis with Certolizumab Pegol Results in Improved Clinical and Patient-Reported Outcomes. *Abstract to be presented at ACR/ARHP*. 2019:8-13.
37. Food and Drug Administration. Center for Drug Evaluation and Research Approval Package for Cimzia (certolizumab pegol). In:2013.

38. Food and Drug Administration. Entresto (sacubitril/valsartan) Package Insert - February 2021. 2021.
39. Solomon SD, McMurray JJ, Anand IS, et al. Angiotensin–neprilysin inhibition in heart failure with preserved ejection fraction. *New England Journal of Medicine*. 2019;381(17):1609-1620.
40. Velazquez EJ, Morrow DA, DeVore AD, et al. Angiotensin–neprilysin inhibition in acute decompensated heart failure. *New England Journal of Medicine*. 2019;380(6):539-548.
41. Solomon SD, Vaduganathan M, L. Claggett B, et al. Sacubitril/valsartan across the spectrum of ejection fraction in heart failure. *Circulation*. 2020;141(5):352-361.
42. Morrow DA, Velazquez EJ, DeVore AD, et al. Clinical outcomes in patients with acute decompensated heart failure randomly assigned to sacubitril/valsartan or enalapril in the PIONEER-HF trial. *Circulation*. 2019;139(19):2285-2288.
43. Ambrosy AP, Braunwald E, Morrow DA, et al. Angiotensin receptor-neprilysin inhibition based on history of heart failure and use of renin-angiotensin system antagonists. *Journal of the American College of Cardiology*. 2020;76(9):1034-1048.
44. Mc Causland FR, Lefkowitz M, Claggett B, et al. Angiotensin-Nepilysin Inhibition and Renal Outcomes in Heart Failure. *Circulation*. 2020;142(Suppl\_3):A17063-A17063.
45. Food and Drug Administration. Cardiovascular and Renal Drugs Advisory Committee – Novartis Briefing Document, December 15, 2020. ENTRESTO® (sacubitril/valsartan) for chronic heart failure and preserved ejection fraction. 2020.
46. Food and Drug Administration. Krystexxa (pegloticase) Package Insert - July 2018. 2018.
47. Sundy JS, Baraf HS, Yood RA, et al. Efficacy and tolerability of pegloticase for the treatment of chronic gout in patients refractory to conventional treatment: two randomized controlled trials. *Jama*. 2011;306(7):711-720.
48. Becker MA, Baraf HS, Yood RA, et al. Long-term safety of pegloticase in chronic gout refractory to conventional treatment. *Annals of the rheumatic diseases*. 2013;72(9):1469-1474.
49. Lawrence Edwards N, Singh JA, Troum O, Yeo AE, Lipsky PE. Characterization of patients with chronic refractory gout who do and do not have clinically apparent tophi and their response to pegloticase. *Rheumatology*. 2019;58(8):1422-1431.
50. Food and Drug Administration. Emflaza (deflazacort) Package Insert - July 2020. 2020.
51. PTC 2020 Annual Report [press release]. 2021.
52. McDonald CM, Sajeev G, Yao Z, et al. Deflazacort vs prednisone treatment for Duchenne muscular dystrophy: a meta - analysis of disease progression rates in recent multicenter clinical trials. *Muscle & nerve*. 2020;61(1):26-35.
53. McDonald CM, Campbell C, Torricelli RE, et al. Ataluren in patients with nonsense mutation Duchenne muscular dystrophy (ACT DMD): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet*. 2017;390(10101):1489-1498.
54. Victor RG, Sweeney HL, Finkel R, et al. A phase 3 randomized placebo-controlled trial of tadalafil for Duchenne muscular dystrophy. *Neurology*. 2017;89(17):1811-1820.
55. Shieh PB, McIntosh J, Jin F, et al. Deflazacort versus prednisone/prednisolone for maintaining motor function and delaying loss of ambulation: a post HOC analysis from the ACT DMD trial. *Muscle & nerve*. 2018;58(5):639-645.
56. Agboola F, Lin GA, Fluetsch N, Walton SM, Rind DM, Pearson SD. The effectiveness and value of Deflazacort and Exon-Skipping therapies for the management of Duchenne muscular dystrophy: a summary from the Institute for Clinical and Economic Review's New England Comparative Effectiveness Public Advisory Council. *Journal of managed care & specialty pharmacy*. 2020;26(4):361-366.

## APPENDIX

## Appendix A. Humira®

**Appendix Table A1. References Submitted by AbbVie**

Citation	Decision
Tzellos T., Song Y., Wang J., Yang H., Singh R., Calimlim B. A longitudinal assessment of the impact of adalimumab on work productivity, skin pain, and quality of life measures among patients with hidradenitis suppurativa. Poster presented at the 28th EADV Congress in Madrid, Spain. October 9-13 2019.	Indication accounts for less than 10% of use
Pleyer U, Almutairi S, Murphy C, Hamam R, Julian K, Hammad S, Nagy O, Habot-Wilner Z, Szepessy Z, Guex-Crosier Y, Androudi S. Impact of Adalimumab (Humira) Therapy on Ocular Inflammation, Selected Health Care Resource Utilization, and Patient-Reported Outcomes in Patients with Active Non-infectious Intermediate, Posterior, or Panuveitis in Routine Clinical Practice [abstract]. <i>Arthritis Rheumatol.</i> 2020; 72 (suppl 10).	Indication accounts for less than 10% of use
Bechera, et al. Efficacy and Safety Results From the SHARPS Study: Phase 4, Randomized, Controlled Trial of Adalimumab Plus Surgery in Moderate-to-Severe Hidradenitis Suppurativa. Oral Presentation at EHSF 2020, Athen	Indication accounts for less than 10% of use
Bechera, et al. Adalimumab in Conjunction With Surgery in Patients With Moderate to Severe Hidradenitis Suppurativa: Baseline Characteristics From a Phase 4, Double-Blind, Randomized, Placebo-Controlled Study. European Hidradenitis Suppurativa Foundation, 5–7 February 2020, Athens, Greec	Indication accounts for less than 10% of use
Croft, et al. Efficacy and Safety of Adalimumab in Pediatric Patients With Moderate to Severe Ulcerative Colitis: Results of a Randomized, Controlled Phase 3 Study. United European Gastroenterology Week, Amsterdam, Netherlands, October 11–13, 2020	Indication accounts for less than 10% of use
Kimball, et al. Impact of Adalimumab on Stabilization or Sustained Improvement in Disease Activity in Moderate to Severe Hidradenitis Suppurativa Patients: An Integrated Analysis of PIONEER Trials. Symposium of Hidradenitis Suppurativa Advances, Nov. 2019; Detroit, Michigan	Indication accounts for less than 10% of use
Zouboulis CC, Okun MM, Prens EP, et al. Long-term adalimumab efficacy in patients with moderate-to-severe hidradenitis suppurativa/acne inversa: 3-year results of a phase 3 open-label extension study. <i>J Am Acad Dermatol.</i> 2019;80(1):60-69.e2.	Indication accounts for less than 10% of use
Hyman JS, et al. The effects of concomitant immunomodulators on the pharmacokinetics, efficacy and safety of adalimumab in paediatric patients with Crohn's disease: a post hoc analysis. <i>Aliment Pharmacol Ther</i> 2019;49(2):155-164	Indication accounts for less than 10% of use
Bettwenworth D, Lee WJ, Clark R, Rath S, Yang M, Cook E, Vavricka S. Anti-TNF treatment effectively reduced rate of hospitalization in patients with inflammatory bowel disease with or without extraintestinal manifestations: real world data in Germany. United European Gastroenterology (UEG) Week 2019, October 19 – 23, 2019, Barcelona, Spain	Intervention/comparison outside our scope
Hawkes JE, Mittal M, Davis M, Brixner D. Impact of Online Prescription Management Systems on Biologic Treatment Initiation. <i>Adv Ther.</i> 2019;36(8):2021-2033.	Intervention/comparison outside our scope
Brixner D, Rubin DT, Mease P, et al. Patient Support Program Increased Medication Adherence with Lower Total Health Care Costs Despite Increased Drug Spending. <i>J Manag Care Spec Pharm.</i> 2019;25(7):770-779.	Intervention/comparison outside our scope

Citation	Decision
Brixner D, Mittal M, Rubin DT, et al. Participation in an innovative patient support program reduces prescription abandonment for adalimumab-treated patients in a commercial population. <i>Patient Prefer Adherence</i> . 2019;13:1545-1556.	Intervention/comparison outside our scope
Afzali A, Dalal S, Griffith J, Guntaka S, Padilla B, Wegrzyn LR. Impact of a Patient Support Program on Inflammatory Bowel Disease-Related Hospitalization in Patients Treated with Adalimumab. <i>Digestive Disease Week (DDW) Annual Meeting</i> , May 2–5, 2020, Chicago, Illinois, USA	Intervention/comparison outside our scope
Warren, et al. Comparison of dermatology quality of life index for novel treatments of moderate-to-severe plaque psoriasis: a network meta-analysis. 28th EADV Congress, October 9–13, 2019, Madrid, Spain	Low-quality evidence
Shear NH, Joshi AD, Zhao J, et al. Comparison of Safety Outcomes for Treatments of Moderate to Severe Plaque Psoriasis through a Network Meta-Analysis. 24th World Congress of Dermatology, 10 – 15 June 2019, Milan, Italy	Low-quality evidence
Rosenberg, et al. Long-Term Drug Survival in Adult Patients With Moderate to Severe Chronic Plaque Psoriasis Treated With Biologic Therapies: Real-World Data From a Large Nationwide Health Maintenance Organization. 29th European Academy of Dermatology and Venereology Congress, 29–31 October 2020, EADV Virtual Congress	Low-quality evidence
Chambers CD, et al. Birth outcomes in women who have taken adalimumab in pregnancy: A prospective cohort study. <i>PLoS ONE</i> 14(10): e0223603. <a href="https://doi.org/10.1371/journal.pone.0223603">https://doi.org/10.1371/journal.pone.0223603</a>	Low-quality evidence
Emery P, Burmester GR, Naredo E, et al. A Phase 4 Trial (PREDICTRA) Assessing the Impact of Residual Inflammation and Clinical Characteristics on the Outcome of Dose Tapering of Adalimumab in Patients With Rheumatoid Arthritis Who Are in Stable Clinical Remission. <i>European Congress of Rheumatology</i> , 12–15 June 2019, Madrid, Spain	Low-quality evidence
Elewaut D, et al. Low Incidence of Inflammatory Bowel Disease Adverse Events in Adalimumab Clinical Trials Across Nine Different Diseases. <i>Arthritis Care Res</i> 2020 Feb 26 10.1002/ACR.24175	Low-quality evidence
MacDougall D, Griffith J, Ehrenberg R, et al. Greater than expected dosing (GTED) assessment among targeted immunomodulators in management of inflammatory bowel disease (IBD). <i>J Manag Care Spec Pharm</i> 2019;25(3a):S76	Outcomes not relevant to our scope
Fumiaki Ueno, Michio Doi, Yumi Kawai, Naoto Ukawa, Jordan Cammarota & Keith A. Betts. Number needed to treat and cost per remitter for biologic treatments of Crohn's disease in Japan, <i>J Med Econ</i> (2020)23:1, 80-85, <a href="https://doi: 10.1080/13696998.2019.1642900">https://doi: 10.1080/13696998.2019.1642900</a>	Outcomes not relevant to our scope
Smolen et al. Disease activity improvements with optimal discriminatory ability between treatment arms: applicability in early and established rheumatoid arthritis clinical trials. <i>Arthritis Research &amp; Therapy</i> (2019) 21:231	Outcomes not relevant to our scope
Skapenko A, et al. Genetic markers associated with clinical and radiographic response in adalimumab plus methotrexate- or methotrexate-treated rheumatoid arthritis patients in OPTIMA. <i>Clin Exp Rheumatol</i> 2019;37(5):783-790	Outcomes not relevant to our scope
Landewé R, Ritchlin CT, Aletaha D, et al. Inhibition of radiographic progression in psoriatic arthritis by adalimumab independent of the control of clinical disease activity. <i>Rheumatology (Oxford)</i> . 2019;58(6):1025-1033.	Outcomes not relevant to our scope
Panaccione R, Colombel JF, Travis SPL, et al. Tight control for Crohn's disease with adalimumab-based treatment is cost-effective: an economic assessment of the CALM trial. <i>Gut</i> . 2020;69(4):658-664.	Outcomes not relevant to our scope

Citation	Decision
Colombel JF, et al. Outcomes and Strategies to Support a Treat-totarget Approach in Inflammatory Bowel Disease: A Systematic Review. <i>Journal of Crohn's and Colitis</i> , 2019, 1–13 doi:10.1093/ecco-jcc/jjz131	Outcomes not relevant to our scope
Spivey CA, Winthrop KL, Griffith J, et al. Retrospective Analysis of the Impact of Adalimumab Initiation on Corticosteroid Utilization and Medical Costs Among Biologic-Naïve Patients with Rheumatoid Arthritis. <i>Rheumatol Ther</i> . 2020;7(1):133-147.	Previously known information about adalimumab related to efficacy
Loftus EV, Reinisch W, Panaccione R, et al. Adalimumab Effectiveness Up to Six Years in Adalimumab-naïve Patients with Crohn's Disease: Results of the PYRAMID Registry. <i>Inflamm Bowel Dis</i> . 2019;25(9):1522-1531.	Previously known information about adalimumab related to efficacy
Pancionne R, et al. Efficacy and Safety of Adalimumab by Disease Duration: Analysis of Pooled Data From Crohn's Disease Studies. <i>Journal of Crohn's and Colitis</i> , 2019, 1–10	Previously known information about adalimumab related to efficacy
Hanuaer S, et al. Rapid Changes in Laboratory Parameters and Early Response to Adalimumab: A Pooled Analysis From Patients With Ulcerative Colitis in Two Clinical Trials. <i>Journal of Crohn's and Colitis</i> , 2019, 1–7 doi:10.1093/ecco-jcc/jjz031	Previously known information about adalimumab related to efficacy
Merola J, Coates L, Lesser EM, et al. The Impact of Psoriasis Severity on Outcomes Among Psoriatic Arthritis Patients Receiving Adalimumab. American College of Rheumatology Annual Meeting, November 8–13, 2019, Atlanta, Georgia	Previously known information about adalimumab related to efficacy
Strand V, Patel P, Chen N, et al. The Impact of Adalimumab vs Placebo on Patient-Reported Outcomes and Utility Measures Among Patients With Moderately to Severely Active Psoriatic Arthritis. American College of Rheumatology Annual Meeting, November 8–13, 2019, Atlanta, Georgia	Previously known information about adalimumab related to efficacy
Behrens F, Tony HP, Koehm M, et al. Sustained improvement in work outcomes in employed patients with rheumatoid arthritis during 2 years of adalimumab therapy: an observational cohort study [published correction appears in <i>Clin Rheumatol</i> . 2020 May 30]. <i>Clin Rheumatol</i> (2020);39(9):2583-2592. <a href="https://doi.org/10.1007/s10067-020-05038-y">https://doi.org/10.1007/s10067-020-05038-y</a>	Previously known information about adalimumab related to efficacy
Ungaro RC, et al. Deep Remission at 1 Year Prevents Progression of Early Crohn's Disease. <i>Gastroenterology</i> 2020 <a href="https://doi.org/10.1053/j.gastro.2020.03.039">https://doi.org/10.1053/j.gastro.2020.03.039</a>	Previously known information about adalimumab related to efficacy
Tektonidou MG, Katsifis G, Georgountzos A, et al. Real-world evidence of the impact of adalimumab on work productivity and sleep measures in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. <i>Ther Adv Musculoskelet Dis</i> . (2020);12:1759720X20949088. <a href="https://doi.org/10.1177/1759720X20949088">https://doi.org/10.1177/1759720X20949088</a>	Previously known information about adalimumab related to efficacy
Van Den Bosch F, Wassenberg S, Zueger P, et al. Impact of prior biologic use on treatment response in patients with rheumatoid arthritis receiving adalimumab in routine clinical care: results from the passion study. <i>Journal of Clinical Rheumatology</i> . 2019;25(3):S54.	Previously known information about adalimumab related to efficacy
Van Den Bosch F, Wassenberg S, Zueger P, et al. Impact of prior biologic use on treatment response in patients with rheumatoid arthritis receiving adalimumab in routine clinical care: Results from the passion study. <i>Journal of Clinical Rheumatology</i> . 2019;25(3):S54.	Previously known information about adalimumab related to efficacy
Nakagawa H, Tanaka Y, Sano S, et al. Real-World Postmarketing Study of the Impact of Adalimumab Treatment on Work Productivity and Activity Impairment in Patients with Psoriatic Arthritis. <i>Adv Ther</i> . 2019;36(3):691-707.	Previously known information about adalimumab related to efficacy



Citation	Decision
Coates LC, Tillett W, D'agostino MA, et.al. Adalimumab Introduction Versus Methotrexate Dose Escalation in Patients with Inadequately Controlled Psoriatic Arthritis: Results from Randomized Phase 4 CONTROL Study. EULAR 2020, e-Congress, June 3-6, 2020	Previously known information about adalimumab related to efficacy
Mease P, Conaghan PG, Tillett W, et al. Maintenance or Achievement of Minimal Disease Activity Following Therapy Optimization With Adalimumab or Methotrexate in Patients With Psoriatic Arthritis: Results From Part 2 of a Randomized, Open-label Phase 4 Study. American College of Rheumatology Convergence, 5-9 November 2020	Previously known information about adalimumab related to efficacy
Harrold LR, Griffith J, Zueger P, et al. Longterm, Real-world Safety of Adalimumab in Rheumatoid Arthritis: Analysis of a Prospective US-based Registry. <i>J Rheumatol</i> . 2020;47(7):959-967.	Previously known information about adalimumab related to efficacy
Savage LJ, Dasgupta D, Reyes-Servin O, Calimlim. Response to adalimumab in patients with plaque psoriasis by associated manifestations: analyses from the British Association of Dermatologists Biologics and Immunomodulators Register. <i>J Eur Acad Dermatol Venereol</i> . 2019; 33 (S3): 4.	Previously known information about adalimumab related to efficacy
Savage LJ, Garcia-Horton V, Li J, Yin L, Betts KA, Calimlim B. Number needed to treat and cost per responder to flexible adalimumab dosing in the treatment of psoriasis in patients with suboptimal response to 40mg every other week dosing. <i>J Eur Acad Dermatol Venereol</i> . 2019;33:3-4	Previously known information about adalimumab related to efficacy
Burmester et al. Long-Term Safety of Adalimumab in 29,967 Adult Patients From Global Clinical Trials Across Multiple Indications: An Updated Analysis. <i>Adv Ther</i> doi.org/10.1007/s12325-019-01145-8	Previously known information about adalimumab related to safety
Fendrick MA, Brixner D, Rubin DT, Mease P, Liu H, Davis M, and Mittal M. Sustained long-term benefits of patient support program participation in immune-mediated diseases: improved medication-taking behavior and lower risk of a hospital visit. <i>Journal of Managed Care &amp; Specialty Pharmacy</i> (2021). <a href="https://doi.org/10.18553/jmcp.2021.20560">https://doi.org/10.18553/jmcp.2021.20560</a>	Study published outside of the timeframe of our review
Bergman M, Patel P, Chen N, Jing Y, Saffore CD. Evaluation of Adherence and Persistence Differences Between Adalimumab Citrate-Free and Citrate Formulations for Patients with Immune-Mediated Diseases in the United States. <i>Rheumatol Ther</i> . 2021;8(1):109-118. doi:10.1007/s40744-020-00256-x	Study published outside of the timeframe of our review
Fendrick, A.M., Macaulay, D., Goldschmidt, D. et al. Higher Medication Adherence and Lower Opioid Use Among Individuals with Autoimmune Disease Enrolled in an Adalimumab Patient Support Program in the United States. <i>Rheumatol Ther</i> (2021). <a href="https://doi.org/10.1007/s40744-021-00309-9">https://doi.org/10.1007/s40744-021-00309-9</a>	Study published outside of the timeframe of our review

\*Seven duplicate references identified and not included.

## Appendix B. Promacta®

---

**Appendix Table B1. References Submitted by Novartis**

Citation	Decision
Ruiz-Negron, Natalia & Crook, Jacob & Rondina, Matthew & Patwardhan, Pallavi & Said, Qayyim & Desai, Isha & Nelson, Richard & Lafleur, Joanne. (2019). Comparing the Risk of Complications for Second-Line Treatments of Immune Thrombocytopenia in Veterans: A U.S. National Study. <i>Blood</i> . 134. 85-85. 10.1182/blood-2019-121894.	Intervention/comparison not relevant to scope
Lal, LS, Said, Q, Andrade, K, Cuker, A. Second-line treatments and outcomes for immune thrombocytopenia: A retrospective study with electronic health records. <i>Res Pract Thromb Haemost</i> . 2020; 4: 1131– 1140. <a href="https://doi.org/10.1002/rth2.12423">https://doi.org/10.1002/rth2.12423</a>	Low-quality evidence
Cai B, Said Q, Li X, Li FY, Arcona S. Healthcare resource use and direct costs in severe aplastic anemia (SAA) patients before and after treatment with eltrombopag. <i>J Med Econ</i> . 2020 Mar;23(3):243-251. doi: 10.1080/13696998.2019.1688820. Epub 2019 Nov 20. PMID: 31686551.	Low-quality evidence



## Appendix C. Tysabri®

**Appendix Table C1. References Submitted by Biogen**

Citation	Decision
Zhovtis-Ryerson L, Foley J, Chang I, et al. Natalizumab extended interval dosing (EID) is associated with a reduced risk of progressive multifocal leukoencephalopathy (PML) than every-4-week (Q4W) dosing: updated analysis of the TOUCH® Prescribing Program database. <i>Neurology</i> . 2020;94(15 suppl):1988	Intervention/comparison not relevant to scope
Chen J, Diouf I, Taylor B, Kalincik T, Van Der Mei I. Effects of natalizumab on patient-reported MS outcomes using prospective data from the Australian MS longitudinal study. Presented at MSVirtual2020: 8th Joint ACTRIMS-ECTRIMS Meeting; September 11–13, 2020. FC04.02	Low-quality evidence
Efthimiou O, Acosta C, Saunders-Hastings P, Pellegrini F. Meta-analysis of randomized controlled trials and real-world evidence comparing natalizumab and fingolimod for relapsing-remitting multiple sclerosis. Presented at MSVirtual2020: 8th Joint ACTRIMS-ECTRIMS Meeting; September 11–13, 2020. P0108	Low-quality evidence
Demortiere S, Rico A, Maarouf A, et al. Maintenance of natalizumab during the first trimester of pregnancy in active multiple sclerosis. <i>Mult Scler</i> . 2020 Mar 23 [Epub ahead of print]	Low-quality evidence
Yeh M, et al. Pregnancy in a modern day multiple sclerosis cohort: Predictors of relapse during pregnancy. Poster (PS12.04), ECTRIMS, 2019, 2020, Washington D.C., US	Low-quality evidence
Landi D, Portaccio E, Bovis F, et al. Continuation of natalizumab versus interruption is associated with lower risk of relapses during pregnancy and postpartum in women with MS. Abstract (338), ECTRIMS, 2019, Stockholm, Sweden	Low-quality evidence
Spelman T, Acosta C, Hyde R, et al. Comparative effectiveness of natalizumab, fingolimod, and first-line therapies for rapidly evolving severe relapsing-remitting multiple sclerosis. Presented at MSVirtual2020: 8th Joint ACTRIMS-ECTRIMS Meeting; September 11–13, 2020. P0859	Low-quality evidence
Peng A, Qiu X, Zhang L, et al. Natalizumab exposure during pregnancy in multiple sclerosis: a systematic review 2019. 396: 202-205	Low-quality evidence
Ghezzi A, Comi G, Grimaldi LM, et al. Pharmacokinetics and pharmacodynamics of natalizumab in pediatric patients with RRMS. <i>Neurol Neuroimmunol Neuroinflamm</i> . 2019;6:e591	Outcomes not relevant to our scope
Hersh C, Kieseier B, de Moor C, Miller D, Campagnolo D, Williams J, et al. Impact of natalizumab on quality of life in a real-world cohort of patients with multiple sclerosis: results from MS PATHS p1036 (poster). Presented at the 8th Joint ECTRIMS meeting 2020; 2020	Previously known information about natalizumab related to efficacy
Julian GS, Rosim RP, Carneseca EC, Rigolon J. Annualized hospitalization rate with natalizumab vs fingolimod in second-line treatment for RRMS in the public healthcare system in Brazil: a claim database approach. <i>PLoS One</i> . 2020;15:e0229768	Previously known information about natalizumab related to efficacy
Cohen M, Mondot L, Bucciarelli F, et al. BEST-MS: A prospective head-to-head comparative study of natalizumab and fingolimod in active relapsing MS. <i>Mult Scler</i> 2020 Oct 30; 1352458520969145 doi: 10.1177/1352458520969145.	Previously known information about natalizumab related to efficacy

Citation	Decision
Butzkueven H, Licata S, Jeffery D, et al. Natalizumab versus fingolimod for patients with active relapsing-remitting multiple sclerosis: results from REVEAL, a prospective, randomised head-to-head study. <i>BMJ Open</i> . 2020;10:e038861	Previously known information about natalizumab related to efficacy
Perumal J, Fox RJ, Balabanov R, et al. Natalizumab is associated with no evidence of disease activity and with improvement in disability and cognitive performance in anti-JC virus seronegative patients with early relapsing-remitting multiple sclerosis: STRIVE 4-year results. <i>Mult Scler</i> . 2019;25(S2):741-742.	Previously known information about natalizumab related to efficacy
Perumal J, Balcer L, Balabanov R, et al. Anti-JC virus seronegative African American patients with early multiple sclerosis treated with natalizumab in STRIVE: a post-hoc analysis. Presented at the Americas Committee for Treatment and Research in Multiple Sclerosis 2020 Forum; February 27–29, 2020; West Palm Beach, FL	Previously known information about natalizumab related to efficacy
Capra R, Morra VB, Mirabella M, et al. Natalizumab is associated with early improvement of working ability in relapsing-remitting multiple sclerosis patients: WANT observational study results. <i>Neurol Sci</i> . 2020 Nov 17 [Epub ahead of print]	Previously known information about natalizumab related to efficacy
Foley J, Carrillo-Infante C, Smith J, Evans K, Ho PR, Lee L, et al. The 5-year Tysabri global observational program in safety (TYGRIS) study confirms the long-term safety profile of natalizumab treatment in multiple sclerosis. <i>Mult Scler Relat Disord</i> . 2019 Nov 21;39:101863	Previously known information about natalizumab related to safety
Wiendl H, Spelman T, Butzkueven H, et al. Real-world disability improvement in patients with relapsing-remitting multiple sclerosis treated with natalizumab in the Tysabri Observational Program. <i>Mult Scler</i> . 2020 Jun 24 [Epub ahead of print]	Previously known information about natalizumab related to safety
Portaccio E, Tudisco L, Pastò L, Razzolini L, Prestipino E, Fonderico M, et al. Pregnancy in women with multiple sclerosis treated with Natalizumab: a re-appraisal of maternal risks in a long-term follow-up. Poster (P409), ECTRIMS, 2019, Stockholm, Sweden	Previously known information about natalizumab related to safety
Ho PR, Koendgen H, Campbell N, Haddock B, Richman S, Chang I. Risk of natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: a retrospective analysis of data from four clinical studies. <i>Lancet Neurol</i> . 2017 Nov;16(11):925-33	Study outside timeframe of review
Lorscheider J, Benkert P, Lienert C, et al. Comparative analysis of natalizumab versus fingolimod as second-line treatment in relapsing-remitting multiple sclerosis. <i>Mult Scler</i> . 2018;24:777-785	Study outside timeframe of review
Kalincik T, Brown JWL, Robertson N, Willis M, Scolding N, Rice CM, et al. Treatment effectiveness of alemtuzumab compared with natalizumab, fingolimod, and interferon beta in relapsing-remitting multiple sclerosis: a cohort study. <i>Lancet Neurol</i> . 2017 Apr;16(4):271-81	Study outside timeframe of review
Kalincik T, Jokubaitis V, Spelman T, et al. Cladribine versus fingolimod, natalizumab and interferon b for multiple sclerosis. <i>Mult Scler</i> . 2018;24:1617-1626	Study outside timeframe of review
Hersh C, Kieseier B, de Moor C, et al. Impact of natalizumab on quality of life in a real-world cohort of patients with multiple sclerosis: results from MS PATHS. <i>Mult Scler J Exp Translation Clin</i> . 2021 April 15 [Epub ahead of print]	Study outside timeframe of review
Zhovtis Ryerson L, Foley J, Kister I, et al. Natalizumab extended interval dosing (EID) is associated with a reduced risk of progressive multifocal leukoencephalopathy (PML) compared with every-4-week (Q4W) dosing:	Study outside timeframe of review

Citation	Decision
updated analysis of the TOUCH® prescribing program database. Neurology. 2021;96(S15):4419	
Plavina T, Fox EJ, Lucas N, Muralidharan KK, Mikol D. A randomized trial evaluating various administration routes of natalizumab in multiple sclerosis. J Clin Pharmacol. 2016;56:1254-1262	Study outside timeframe of review
Trojano M, Ramio-Torrenta L, Grimaldi LM, Lubetzki C, Schippling S, Evans KC, et al. A randomized study of natalizumab dosing regimens for relapsing-remitting multiple sclerosis. Mult Scler. 2021 Apr 6:13524585211003020	Study outside timeframe of review
Perumal J, Fox RJ, Balabanov R, et al. Natalizumab is associated with no evidence of disease activity and improved cognitive function and health-related quality of life in anti-JC virus seronegative patients with early relapsing-remitting multiple sclerosis: a 3-year analysis of STRIVE. Mult Scler. 2018;24(S2):477-478. P891	Study outside timeframe of review
Chen J, Taylor BV, Blizzard L et al. Effects of multiple sclerosis disease-modifying therapies on employment measures using patient reported data. J. Neurol Neurosurg Psychiatry. 2018 [Epub ahead of print] [2018;89:1200-1207].doi:10.1136/jnnp-2018-318228	Study outside timeframe of review
Margoni M, Rinaldi F, Riccardi A, Franciotta S, Perini P, Gallo P. No evidence of disease activity including cognition (NEDA-3 plus) in naive pediatric multiple sclerosis patients treated with natalizumab. J Neurol. 2020 Jan;267(1):100-5	Study population outside approved label indication
Butzkueven H, Kappos L, Wiendl H, et al. Long-term safety and effectiveness of natalizumab treatment in clinical practice: 10 years of real-world data from the Tysabri Observational Program (TOP). J Neurol Neurosurg Psychiatry. 2020;91:660-668.	Previously known information about natalizumab related to efficacy/safety
Perumal J, Balabanov R, Balcer L, et al. Disability improvement in early multiple sclerosis patients treated with natalizumab in STRIVE, a phase 4, multicenter observational study. Presented at the Americas Committee for Treatment and Research in Multiple Sclerosis 2020 Forum; February 27–29, 2020; West Palm Beach, FL	Previously known information about natalizumab related to efficacy
Zhovtis-Ryerson L, Frohman TC, Foley J, et al. Extended interval dosing of natalizumab in multiple sclerosis. J Neurol Neurosurg Psychiatry. 2016 Aug; 87(8):885-9	Study outside timeframe of review
Kagstrom S, Falt A, Forsberg L, Berglund A, Hillert J, Nilsson P, et al. Improved clinical outcomes in patients treated with Natalizumab for at least 8 years – real-world data from a Swedish national post-marketing surveillance study (IMSE 1). Poster (P1383),ECTRIMS, 2019, Stockholm, Sweden	Previously known information about natalizumab related to efficacy/safety

\*One duplicate reference identified and not included.

## Appendix D. Xifaxan®

**Appendix Table D1. References Submitted by Bausch Health**

Citation	Decision
Shah ED, Salwen-Deremer JK, Gibson PR, Muir JG, Eswaran S, Chey WD. Comparing costs and outcomes of treatments for irritable bowel syndrome with diarrhea: cost-benefit analysis [published online ahead of print October 1, 2020]. <i>Clin Gastroenterol Hepatol</i> . 2020.	Low-quality evidence
Frenette CT. Lack of colonic microbial cross-resistance to other antibiotics in patients treated with rifaximin alone vs rifaximin plus lactulose for reducing the risk of overt hepatic encephalopathy (OHE) recurrence. Presented at: American College of Gastroenterology; Virtual; October 23-28, 2020.	Intervention/comparison not relevant to scope
Tapper EB, Aberasturi D, Zhao Z, Hsu CY, Parikh ND. Outcomes after hepatic encephalopathy in population-based cohorts of patients with cirrhosis. <i>Aliment Pharmacol Ther</i> . 2020;51(12):1397-1405.	Low-quality evidence
Ishikawa T, Endo S, Imai M, et al. Changes in the body composition and nutritional status after long-term rifaximin therapy for hyperammonemia in Japanese patients with hepatic encephalopathy. <i>Intern Med</i> . 2020;59(20):2465-2469.	Low-quality evidence
Jesudian AB, Ahmad M, Bozkaya D, Migliaccio-Walle K. Cost-effectiveness of rifaximin treatment in patients with hepatic encephalopathy. <i>J Manag Care Spec Pharm</i> . 2020;26(6):750-757	Low-quality evidence
Oey RC, Buck LEM, Erler NS, van BuurenHR, de Man RA. The efficacy and safety of rifaximin-alpha: a 2-year observational study of overt hepatic encephalopathy. <i>Therap Adv Gastroenterol</i> . 2019;12:1756284819858256.	Previously known information about rifaximin related to efficacy
Zhuang X, Tian Z, Luo M, Xiong L. Short-course rifaximin therapy efficacy and lactulose hydrogen breath test in Chinese patients with diarrhea-predominant irritable bowel syndrome. <i>BMC Gastroenterol</i> . 2020;20(1):187.	Previously known information about rifaximin related to efficacy
Chautant F, Guillaume M, Robic MA, et al. Lessons from "real life experience" of rifaximin use in the management of recurrent hepatic encephalopathy. <i>World J Hepatol</i> . 2020;12(1):10-20	Previously known information about rifaximin related to efficacy
Suzuki H, Sezaki H, Suzuki F, et al. Real-world effects of long-term rifaximin treatment for Japanese patients with hepatic encephalopathy. <i>Hepatol Res</i> . 2019;49(12):1406-1413.	Previously known information about rifaximin related to efficacy
Salehi S, Tranah TH, Lim S, et al. Rifaximin reduces the incidence of spontaneous bacterial peritonitis, variceal bleeding and all-cause admissions in patients on the liver transplant waiting list. <i>Aliment Pharmacol Ther</i> . 2019;50(4):435-441.	Previously known information about rifaximin related to efficacy
Lembo A, Rao SSC, Heimanson Z, Pimentel M. Abdominal Pain Response to Rifaximin in Patients With Irritable Bowel Syndrome With Diarrhea. <i>Clinical and Translational Gastroenterology</i> . 2020;11(3): e00144.	Previously known information about rifaximin related to efficacy
Volk ML, Burne R, Guerin A, et al. Hospitalizations and healthcare costs associated with rifaximin versus lactulose treatment among commercially insured patients with hepatic encephalopathy in the United States. <i>J Med Econ</i> . 2021;24(1):202-211.	Study published outside of the timeframe of our review

## Appendix E. Trokendi XR®

**Appendix Table E1. References Identified by ICER Systematic Literature Review**

Citation	Decision
Lee SK, Lee SA, Kim DW, et al. A randomized, open-label, multicenter comparative trial of levetiracetam and topiramate as adjunctive treatment for patients with focal epilepsy in Korea. <i>Epilepsy Behav.</i> 2019;97:67-74.	Previously known information about topiramate related to efficacy
Yi, Z.,Wu, H.,Yu, X, et al. High-dose prednisone therapy for infantile spasms and late-onset epileptic spasms in China: The addition of topiramate provides no benefit. <i>Seizure.</i> 2019. 71:174-178	Study population outside approved label indication
Ehrlich, M.,Reuter, U.,Gendolla, A.,Heinze, A.,Klatt, J.,Wen, S.,Groth, M.,Koch, M.,Maier-Peuschel, M.,Hentschke, C. Characteristics of the first head-to-head randomized, double-blind, double-dummy trial of erenumab and topiramate for the prevention of episodic and chronic migraine. <i>European Journal of Neurology.</i> 2020. 27:13	Study protocol
Rothrock JF, Adams AM, Lipton RB, et al. FORWARD Study: Evaluating the Comparative Effectiveness of OnabotulinumtoxinA and Topiramate for Headache Prevention in Adults With Chronic Migraine. <i>Headache.</i> 2019;59(10):1700-1713. doi:10.1111/head.13653	New evidence of no clinical benefit with topiramate (vs. another treatment)
Blumenfeld, A. M.,Patel, A. T.,Turner, I. M.,Mullin, K. B.,Manack Adams, A.,Rothrock, J. F. Patient-Reported Outcomes from a 1-Year, Real-World, Head-to-Head Comparison of OnabotulinumtoxinA and Topiramate for Headache Prevention in Adults With Chronic Migraine. <i>Journal of primary care &amp; community health.</i> 2020. 11:2150132720959936	New evidence of no clinical benefit with topiramate (vs. another treatment)

## Appendix F. Venclexta®

**Appendix Table F1. References Submitted by AbbVie**

Citation	Decision
Pratz et al. Management of neutropenia during venetoclax-based combination treatment in patients with newly diagnosed acute myeloid leukemia. 61st American Society of Hematology Annual Meeting and Exposition; December 7-10, 2019; Orlando, FL. Poster 3897.	Intervention/comparison not relevant to scope
Chyla et al. Response to venetoclax in combination with low intensity therapy (LDAC or HMA) in untreated patients with acute myeloid leukemia patients with IDH, FLT3 and other mutations and correlations with BCL2 family expression. 61st American Society of Hematology Annual Meeting and Exposition; December 7-10, 2019; Orlando, FL.	Intervention/comparison not relevant to scope
Jonas et al. Timing of response to venetoclax combination treatment in older patients with acute myeloid leukemia. American Society of Clinical Oncology (ASCO) Annual Meeting; May 29-31, 2020; Virtual Scientific Program. Poster 304.	Intervention/comparison not relevant to scope
Sharman, et al. Phase 3b study to evaluate debulking regimens prior to initiating venetoclax therapy in untreated patients with chronic lymphocytic leukemia. European Hematology Association (EHA) 25th Annual Meeting; June 11–14, 2020. Virtual Edition. Poster Presentation EP687.	Intervention/comparison not relevant to scope
Flinn, et al. Debulking regimens prior to initiating venetoclax therapy in untreated patients with chronic lymphocytic leukemia: interim results from a phase 3b study. 62nd ASH Annual Meeting and Exposition; December 5-8, 2020; All-Virtual Meeting. Poster 3151.	Intervention/comparison not relevant to scope
Konodo T, et al. Real-World Treatment Patterns and Clinical Outcomes in Unfit Patients with AML Receiving First-Line Systemic Treatment or Best Supportive Care (CURRENT): Final Analysis. Blood (2020) 136 (Supplement 1): oral abstract	Intervention/comparison not relevant to scope
Pardee T, et al. Treatment Patterns and Outcomes of Patients with Newly Diagnosed Acute Myeloid Leukemia (AML) Treated with Hypomethylating Agents (HMA) in the United States (US). Blood (2020) 136 (Supplement 1): 14–16	Intervention/comparison not relevant to scope
Sharman, JP., et al. "Debulking eliminates need for hospitalization prior to initiating frontline venetoclax therapy in previously untreated CLL patients: a phase 3b study." (2019): 3042-3042.	Intervention/comparison not relevant to scope
Harrup, et al. Efficacy of subsequent novel targeted therapies, including repeated venetoclax-rituximab (VenR), in patients with relapsed/refractory chronic lymphocytic leukemia (R/R CLL) previously treated with fixed-duration VenR in the MURANO study. 62nd ASH Annual Meeting and Exposition; December 5-8, 2020; All-Virtual Meeting. Poster 3139	Intervention/comparison not relevant to scope
Durno, et al. Cost-effectiveness of a 24-month fixed duration of venetoclax in combination with rituximab in relapsed/refractory chronic lymphocytic leukemia. International Workshop Chronic Lymphocytic Leukemia; September 20-23, 2019. Edinburgh, Scotland	Low-quality evidence
Davids, et al. Cost-effectiveness of a 12-month fixed duration of venetoclax in combination with obinutuzumab in first-line chronic lymphocytic leukemia in the United States. 61st American Society of Hematology Annual Meeting and Exposition; December 7-10, 2019; Orlando, FL. Poster 4741.	Low-quality evidence



Citation	Decision
Cho, et al. Budget Impact of 12-month Fixed Treatment Duration Venetoclax in Combination with Obinutuzumab in Previously Untreated Chronic Lymphocytic Leukemia (CLL) Patients in the United States. <i>Cho Pharmacoeconomics</i> , 38(9), 941-951. DOI: 10.1007/s40273-020-00919-1	Low-quality evidence
Cho, et al. Total cost of care with 12 months fixed duration of venetoclax + obinutuzumab in previously-untreated chronic lymphocytic leukemia (CLL) patients. International Workshop Chronic Lymphocytic Leukemia; September 20-23, 2019. Edinburgh, Scotland. Poster Presentation 1976.	Low-quality evidence
Shadman et al. Treatment discontinuation patterns for patients with CLL in the real-world settings: results from a multi-center study. 61st American Society of Hematology Annual Meeting and Exposition; December 7-10, 2019; Orlando, FL. Poster 3048.	Low-quality evidence
Wei, et al. Venetoclax combined with low-dose cytarabine for previously untreated patients with acute myeloid leukemia: results from a Phase Ib/II study. Wei AH, et al. <i>J Clin Oncol</i> . Doi.org/10.1200/JCO.18.01600	Low-quality evidence
Kater, et al. Efficacy of venetoclax in patients with relapsed/refractory chronic lymphocytic leukemia: An open-label, single arm, multi-center, Phase 3b trial (VENICE I). European Hematology Association (EHA) 25th Annual Meeting; June 11–14, 2020. Virtual Edition.	Low-quality evidence
Anderson, et al. Neutropenia analysis of venetoclax monotherapy in patients with relapsed or refractory chronic lymphocytic leukemia: Pooled data from VENICE-I and -II phase IIIb trials. American Society of Clinical Oncology (ASCO) Annual Meeting; May 29-31, 2020; Virtual Scientific Program. Abstract published only.	Low-quality evidence
Cochrane, et al. Impact of venetoclax monotherapy on the quality of life of patients with relapsed or refractory chronic lymphocytic leukemia: results from VENICE II Phase 3b trial. European Hematology Association (EHA) 25th Annual Meeting; June 11–14, 2020. Virtual Edition. Poster Presentation EP701.	Low-quality evidence
Konopleva, et al. Results of venetoclax and azacytidine combination in chemotherapy ineligible untreated patients with acute myeloid leukemia with FLT3 mutations. 62nd ASH Annual Meeting and Exposition; December 5-8, 2020; All-Virtual Meeting. Poster 1904.	Low-quality evidence
Perl, et al. Venetoclax in combination with gilteritinib in patients with relapsed/refractory acute myeloid leukemia: a Phase 1b study. 61st American Society of Hematology Annual Meeting and Exposition; December 7-10, 2019; Orlando, FL. Poster 3910.	Low-quality evidence
Daver, et al. Efficacy and safety of venetoclax in combination with gilteritinib for relapsed/refractory FLT3-mutated acute myeloid leukemia in the expansion cohort of a phase 1b study. 62nd ASH Annual Meeting and Exposition; December 5-8, 2020; All-Virtual Meeting. Oral Presentation 333.	Low-quality evidence
Sudhapalli, P., M. Piena, and A. Palaka. "Systematic literature review and network meta-analysis comparing therapies for treatment-naïve patients with Chronic Lymphocytic Leukemia." E-Poster presented at: European Hematology Association Annual Congress. 2020.	Low-quality evidence
Kater, et al. Minimal residual disease response with venetoclax monotherapy in relapsed/refractory CLL patients: VENICE I, Phase 3b exploratory analysis. International Workshop Chronic Lymphocytic Leukemia; September 20-23, 2019. Edinburgh, Scotland. Poster Presentation 2029.	Low-quality evidence
Mato A, et al. Treatment sequences and outcomes of patients with CLL treated with venetoclax and other novel agents post introduction of novel therapies.	Outcomes not relevant to our scope

Citation	Decision
61st American Society of Hematology Annual Meeting and Exposition; December 7-10, 2019; Orlando, FL. Poster 1756.	
Mato A, et al. Efficacy of Therapies Following Venetoclax Discontinuation in CLL: Focus on B-Cell Receptor Signal Transduction Inhibitors and Cellular Therapies. 60th American Society of Hematology Annual Meeting and Exposition; December 7-10, 2019; Orlando, FL.	Outcomes not relevant to our scope
Thompson, et al. Venetoclax Re-Treatment of Chronic Lymphocytic Leukemia (CLL) Patients after a Previous Venetoclax-Based Regimen. Blood (2020) 136 (Supplement 1): 39–41	Outcomes not relevant to our scope
Rhodes, et al. Factors impacting treatment selection in treatment-naïve patients with CLL: a multicenter study. European Hematology Association (EHA) 24th Annual Meeting; June 13–16, 2019; Amsterdam, The Netherlands. Poster PF381.	Outcomes not relevant to our scope
Mato A, et al. The impact of early discontinuation/dose modification of venetoclax on outcomes in patients with relapsed/refractory chronic lymphocytic leukemia: post-hoc analyses from the phase III MURANO study. Mato AR, et al. Haematologica. 2020;Online ahead of print. doi: 10.3324/haematol.2020.266486. PMID: 33327712.	Outcomes not relevant to our scope
Wu J., et al. "Impact of major genomic alterations on outcome of relapsed/refractory chronic lymphocytic leukemia patients receiving venetoclax plus rituximab in the phase 3 Murano Study." Hematological Oncology 37 (2019): 106-108.	Outcomes not relevant to our scope
Mato A, et al. Impact of premature venetoclax (Ven) discontinuation/interruption on outcomes in relapsed/ refractory (R/R) chronic lymphocytic leukemia (CLL): Phase III MURANO study results. American Society of Clinical Oncology (ASCO) Annual Meeting; May 29-31, 2020; Virtual Scientific Program. Poster 361.	Outcomes not relevant to our scope
Pratz et al. Outcomes after stem cell transplant in older patients with acute myeloid leukemia treated with venetoclax-based therapies. 61st American Society of Hematology Annual Meeting and Exposition; December 7-10, 2019; Orlando, FL.	Outcomes not relevant to our scope
Tausch, et al. Genetic markers and outcome in the CLL14 trial of the GCLLSG comparing front line obinutuzumab plus chlorambucil or venetoclax in patients with comorbidity. European Hematology Association (EHA) 24th Annual Meeting; June 13–16, 2019; Amsterdam, The Netherlands.	Outcomes not relevant to our scope
Al-Sawaf, Othman, et al. "Prevention and management of tumor lysis syndrome in patients with CLL and coexisting conditions treated with venetoclax-obinutuzumab or chlorambucil-obinutuzumab: results from the randomized CLL14 trial." (2019): 4315-4315.	Outcomes not relevant to our scope
Fischer, et al. Quantitative analysis of minimal residual disease (MRD) shows high rates of undetectable MRD after fixed-duration chemotherapy-free treatment and serves as surrogate marker for progression-free survival: A prospective analysis of the randomized CLL14 trial. 61st American Society of Hematology Annual Meeting and Exposition; December 7-10, 2019; Orlando, FL.	Outcomes not relevant to our scope
Al-Sawaf, et al. Clonal dynamics after venetoclax-obinutuzumab therapy: Novel insights from the randomized, phase 3 CLL14 trial. 62nd ASH Annual Meeting and Exposition; December 5-8, 2020; All-Virtual Meeting.	Outcomes not relevant to our scope
Jonas, et al. Use of anti-infection CYP3A inhibitors and impact of these agents on outcomes in patients with acute myeloid leukemia treated with venetoclax	Outcomes not relevant to our scope



Citation	Decision
plus azacitidine on the VIALE-A study. 62nd ASH Annual Meeting and Exposition; December 5-8, 2020; All-Virtual Meeting. Poster 2846.	
Mato A, et al. Assessment of the Efficacy of Therapies Following Venetoclax Discontinuation in CLL Reveals BTK inhibition as an Effective Strategy.Cancer Res. 2020 Jul 15;26(14):3589-3596. doi: 10.1158/1078-0432.CCR-19-3815. Epub 2020 Mar 20.	Outcomes not relevant to our scope
Keruakous, et al. Venetoclax-induced tumor lysis syndrome in acute myeloid leukemia: Real world experience. American Society of Clinical Oncology (ASCO) Annual Meeting; May 29-31, 2020; Virtual Scientific Program.	Outcomes not relevant to our scope
Eckert et al. Venetoclax exposure-efficacy and exposure-safety relationships in subjects with treatment-naïve acute myeloid leukemia who are ineligible for intensive chemotherapy. 62nd ASH Annual Meeting and Exposition; December 5-8, 2020; All-Virtual Meeting. Poster 2847	Previously known information about venetoclax related to efficacy
Pollyea et al. Characteristics and Outcomes of Newly Diagnosed Acute Myeloid Leukemia Patients Receiving Venetoclax Combinations vs Other Therapies: Results from the AML Real world evidenCe (ARC) Initiative. Blood (2020) 136 (Supplement 1): 26–28	Previously known information about venetoclax related to efficacy
Talati et al. TREATMENT PATTERNS AND OUTCOMES OF NEWLY DIAGNOSED ACUTE MYELOID LEUKEMIA PATIENTS RECEIVING VENETOCLAX COMBINATIONS VS OTHER THERAPIES: RESULTS FROM THE AML REAL WORLD EVIDENCE (ARC) INITIATIVE. EHA Library. Talati C. 06/12/20; 297747; PB1831	Previously known information about venetoclax related to efficacy
Zheng et al. Venetoclax Effectiveness, Safety, and Treatment Patterns in Chronic Lymphocytic Leukemia Patients: Results from the CLL Collaborative Study of Real-World Evidence (CORE). Blood (2020) 136 (Supplement 1): 31–32.	Previously known information about venetoclax related to efficacy
Flinn et al. Phase 1b Study of venetoclax - obinutuzumab in previously untreated and relapsed/refractory chronic lymphocytic leukemia. Blood 2019 ; 133 (26): 2765-2775	Previously known information about venetoclax related to efficacy
Kater AP, et al. Fixed duration of venetoclax-rituximab in relapsed/refractory chronic lymphocytic leukemia eradicates minimal residual disease and prolongs survival: post-treatment follow-up of the MURANO phase III study. J Clin Oncol. 2019;37(4):269-277	Previously known information about venetoclax related to efficacy
Kater AP, et al. Venetoclax plus rituximab in relapsed chronic lymphocytic leukemia: 4-year results and evaluation of impact of genomic complexity and gene mutations from the MURANO phase III study. J Clin Oncol. 2020 Sept 28. doi:10.1200/JCO.20.00948	Previously known information about venetoclax related to efficacy
Seymour et al. Time-limited venetoclax-rituximab in relapsed/refractory chronic lymphocytic leukemia: first presentation of 4-year data from the MURANO study. International Workshop Chronic Lymphocytic Leukemia; September 20-23, 2019. Edinburgh, Scotland. Poster Presentation 2266	Previously known information about venetoclax related to efficacy
Al-Sawaf O, et al. Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2020; 21:1188-1200	Previously known information about venetoclax related to efficacy
Al-Sawaf, Othman, et al. "Fixed-duration venetoclax-obinutuzumab for previously untreated patients with chronic lymphocytic leukemia: Follow-up of efficacy and safety results from the multicenter, open-label, randomized, phase III CLL14 trial." (2020): 8027-8027.	Previously known information about venetoclax related to efficacy
Pollyea, et al. Results of venetoclax and azacytidine combination in chemotherapy ineligible untreated patients with acute myeloid leukemia with	Previously known information about venetoclax related to efficacy

Citation	Decision
IDH 1/2 mutations. 62nd ASH Annual Meeting and Exposition; December 5-8, 2020; All-Virtual Meeting.	
Pratz, et al. Delays in Time to Deterioration of HRQoL Observed in Patients With Acute Myeloid Leukemia Receiving Venetoclax in Combination with Azacitidine or in Combination With Low-Dose Cytarabine. Blood (2020) 136 (Supplement 1): 33-35	Previously known information about venetoclax related to efficacy
Wei, et al. A Phase 3 study of venetoclax plus low-dose cytarabine in previously untreated older patients with acute myeloid leukemia (VIALE-C): a 6-month update. American Society of Clinical Oncology (ASCO) Annual Meeting; May 29-31, 2020; Virtual Scientific Program. Poster 284.	Previously known information about venetoclax related to efficacy
Wolach O, et al. First Results from a Nationwide Prospective Non-Interventional Study of Venetoclax-Based 1st Line Therapies in Patients with Acute Myeloid Leukemia (AML) - Revive Study. Blood (2020) 136 (Supplement 1): 27-28	Previously known information about venetoclax related to efficacy
Donnellan W, et al. Use of Venetoclax (VEN) and Hypomethylating Agents (HMA) in Newly Diagnosed Acute Myeloid Leukemia (AML) in the United States (US) – Real World (RW) Response, Treatment Duration, Dose and Schedule Modifications. Blood (2020) 136 (Supplement 1): 11-12	Previously known information about venetoclax related to efficacy
Seymour, et al. Four-year analysis of MURANO study confirms sustained benefit of time-limited venetoclax-rituximab (VenR) in relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL). Presented at the 61st American Society of Hematology Annual Meeting and Exposition; December 7-10, 2019; Orlando, FL.	Previously known information about venetoclax related to efficacy
Kater, et al. Five-year analysis of MURANO study demonstrate enduring undetectable minimal residual disease (uMRD) in a subset of relapsed/refractory chronic lymphocytic leukemia (R/R CLL) patients following fixed-duration venetoclax-rituximab (VenR) therapy. 62nd ASH Annual Meeting and Exposition; December 5-8, 2020; All-Virtual Meeting.	Previously known information about venetoclax related to efficacy
Wei, et al. Long-term follow up: Phase Ib/II study of venetoclax plus low-dose cytarabine in previously untreated older adults with acute myeloid leukemia ineligible for intensive chemotherapy. European Hematology Association (EHA) 25th Annual Meeting; June 11-14, 2020. Virtual Edition. Poster Presentation EP554.	Previously known information about venetoclax related to safety
Karol, et al. Safety, efficacy, and PK of the BCL2 inhibitor venetoclax in combination with chemotherapy in pediatric and young adult patients with relapsed/refractory acute myeloid leukemia and acute lymphoblastic leukemia: Phase 1 study. 61st American Society of Hematology Annual Meeting and Exposition; December 7-10, 2019; Orlando, FL. Poster 2649.	Study population outside approved label indication
Karol, et al. Venetoclax alone or in combination with chemotherapy: responses in pediatric patients with relapsed/refractory acute myeloid leukemia with heterogenous genomic profiles. 62nd ASH Annual Meeting and Exposition; December 5-8, 2020; All-Virtual Meeting. Poster 1030.	Study population outside approved label indication
Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma v4.2021. NCCN Clinical Practice Guidelines in Oncology	Study published outside of the timeframe of our review
Acute Myeloid Leukemia v3.2021. NCCN Clinical Practice Guidelines in Oncology	Study published outside of the timeframe of our review
Ito T, et al. Patterns of Healthcare Resource Utilization (HRU) in Unfit Patients With Acute Myeloid Leukemia (AML) Receiving First-line Systemic Treatment or Best Supportive Care (BSC): A Multicenter International Study (CURRENT). Presented at ISPOR 2021 May	Study published outside of the timeframe of our review

Citation	Decision
Leblanc T, et al. Budget Impact Analysis of Venetoclax Combination Treatments in Newly Diagnosed Acute Myeloid Leukemia in Adults Who are Ineligible for Intensive Chemotherapy. J Manag Care Spec Pharm 2021;27(4a):C41	Study published outside of the timeframe of our review
Davids, et al. The Economic Impact of Treatment Sequences for Chronic Lymphocytic Leukemia (CLL) in the United States: A Cost of Care and Budget Impact Model of Venetoclax plus Obinutuzumab Sequences for CLL Patients. J Manag Care Spec Pharm, 2021 Apr;27(4-a Suppl):S1-S152.	Study published outside of the timeframe of our review

## Appendix G. Lupron Depot®

**Appendix Table G1. References Submitted by AbbVie**

Citation	Decision
Klein KO, Soliman AM, Grubb EB, Nisbet P. A survey of care pathway and health-related quality of life impact for children with central precocious puberty. <i>Curr Med Res Opin.</i> 2020;36(3):411-418. doi:10.1080/03007995.2019.1699517	Intervention/comparison not relevant to our scope
Klein K, Soliman AM, Bonafede M, Nelson JK, Grubb E. Health care utilization and economic burden in patients with central precocious puberty: An assessment of the commercially insured and medicaid populations. <i>J Manag Care Spec Pharm.</i> 2019;25(7):836-846. doi:10.18553/jmcp.2019.25.7.836	Intervention/comparison not relevant to our scope
Small EJ, Saad F, Chowdhury S, et al. Apalutamide and overall survival in non-metastatic castration-resistant prostate cancer. <i>Ann Oncol.</i> 2019;30(11):1813-1820. doi:10.1093/annonc/mdz397	Intervention/comparison not relevant to scope
Smith MR, Saad F, Chowdhury S, et al. Apalutamide and Overall Survival in Prostate Cancer. <i>Eur Urol.</i> 2021;79(1):150-158. doi:10.1016/j.eururo.2020.08.011	Intervention/comparison not relevant to scope
Sternberg CN, Fizazi K, Saad F, et al. Enzalutamide and Survival in Nonmetastatic, Castration-Resistant Prostate Cancer. <i>N Engl J Med.</i> 2020;382(23):2197-2206. doi:10.1056/nejmoa2003892	Intervention/comparison not relevant to scope
Fizazi K, Shore N, Tammela TL, et al. Darolutamide in Nonmetastatic, Castration-Resistant Prostate Cancer. <i>N Engl J Med.</i> 2019;380(13):1235-1246. doi:10.1056/NEJMoa1815671	Intervention/comparison not relevant to scope
Davis ID, Martin AJ, Stockler MR, et al. Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer. <i>N Engl J Med.</i> 2019;381(2):121-131. doi:10.1056/nejmoa1903835	Intervention/comparison not relevant to scope
Chi KN, Agarwal N, Bjartell A, et al. Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer. <i>N Engl J Med.</i> 2019;381(1):13-24. doi:10.1056/NEJMoa1903307	Intervention/comparison not relevant to scope
Armstrong AJ, Szmulewitz RZ, Petrylak DP, et al. Arches: A randomized, phase III study of androgen deprivation therapy with enzalutamide or placebo in men with metastatic hormone-sensitive prostate cancer. <i>J Clin Oncol.</i> 2019;37(32):2974-2986. doi:10.1200/JCO.19.00799	Intervention/comparison not relevant to scope
Klein KO, Soliman AM, Bonafede M, Nelson JK, Grubb E. Treatment patterns, health resource utilization and costs among central precocious puberty patients treated with leuprolide or histrelin: an examination of the commercial and Medicaid populations. <i>J Med Econ.</i> 2020;23(4):407-414. doi:10.1080/13696998.2019.1697700	Low-quality evidence
Fujita LGA, Palhares HM da C, da Silva AP, Tomé JM, Borges M de F. Clinical and laboratory parameters of gonadotropin-releasing hormone analog treatment effectiveness in children with precocious puberty. <i>Clinics.</i> 2019;74:1-7. doi:10.6061/clinics/2019/e1205	Outcomes not relevant to our scope
Chung BH, Horie S, Chiong E. Clinical studies investigating the use of leuprorelin for prostate cancer in Asia. <i>Prostate Int.</i> 2020;8(1):1-9. doi:10.1016/j.pnil.2019.06.001	Previously known information about leuprolide acetate related to efficacy
Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in Metastatic Prostate Cancer before Chemotherapy. <i>N Engl J Med.</i> 2014;371(5):424-433. doi:10.1056/nejmoa1405095	Study published outside of the timeframe of our review

Citation	Decision
Hussain M, Fizazi K, Saad F, et al. Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer. N Engl J Med. 2018;378(26):2465-2474. doi:10.1056/nejmoa1800536	Study published outside of the timeframe of our review
Smith MR, Saad F, Chowdhury S, et al. Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer. N Engl J Med. 2018;378(15):1408-1418. doi:10.1056/nejmoa1715546	Study published outside of the timeframe of our review
Trujillo MV, 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;34(6):733-739. doi:10.1515/jpem-2021-0114	Study published outside of the timeframe of our review

## Appendix H. Cimzia®

**Appendix Table H1. References Submitted by UCB**

Citation	Decision
Mueller RB, Spaeth M, Restorff C, et al. Superiority of a Treat-to-Target Strategy over Conventional Treatment with Fixed csDMARD and Corticosteroids: A Multi-Center Randomized Controlled Trial in RA Patients with an Inadequate Response to Conventional Synthetic DMARDs, and New Therapy with Certolizumab Pegol [Manuscript]. J Clin Med;2019;8;3:302	Intervention/comparison not relevant to scope
Landewé R, van der Heijde D, Dougados M, et al. Efficacy Outcomes in Certolizumab Pegol-Treated Patients with Axial Spondyloarthritis in Asia: Results from Part A of C-OPTIMISE [Poster]. Int J Rheum Dis. 2019;22(S3):83.	Low-quality evidence
Landewé R, van der Heijde D, Dougados M, et al. Maintenance of Clinical Remission in Early Axial Spondyloarthritis Following Certolizumab Pegol Dose Reduction [Manuscript]. Ann Rheum Dis. 2020;79(7):920-928	Low-quality evidence
Landewé R, van der Heijde D, Dougados M, et al. Induction of Sustained Clinical Remission in Early Axial Spondyloarthritis following Certolizumab Pegol Treatment: 48-Week Outcomes from C-OPTIMISE [Manuscript]. Rheumatol Ther. 2020;7(3):581-599	Low-quality evidence
van der Horst-Bruinsma I, van Bentuearm R, Verbraak FD, et al. The Impact of Certolizumab Pegol Treatment on the Incidence of Anterior Uveitis Flares in Patients with Axial Spondyloarthritis: 48-Week Interim Results from C-VIEW [Manuscript]. RMD Open. 2020;6(1):e001161	Low-quality evidence
Tillett WR, Coates LC, Nurminen T, et al. Stringent Thresholds of Disease Control are Associated with Reduced Burden on Paid and Household Work Productivity in Patients with Psoriatic Arthritis During Long-Term Treatment with Certolizumab Pegol [Abstract]. Value Health. 2020;23(Suppl 2):S411..	Outcomes not relevant to our scope
Blauvelt A, Gottlieb AB, Fierens F, et al. Dose Adjustment Patterns in the Open-Label Extension Arms of Three Phase 3 Trials of Certolizumab Pegol in Psoriasis: CIMPASI-1, CIMPASI-2, and CIMPACT [Poster]. SKIN The Journal of Cutaneous Medicine. 2020;4(6):S85	Outcomes not relevant to our scope
Szekanecz Z, Koncz Á, Dunkel J, et al. Cigarette Smoking and Clinical Response to Certolizumab Pegol Treatment in Hungarian, Czech, and Slovak Patients with Rheumatoid Arthritis: 104-week data from the CIMDORA prospective, non-interventional study [Manuscript]. Clin Exper Rheum. 2019 Apr 9;37:1010-1018	Outcomes not relevant to scope
Coates LC, Merola JF, Fitzgerald O, et al. Achievement of PASDAS Low Disease Activity and Very Low Disease Activity in Patients with Psoriatic Arthritis Treated with Certolizumab Pegol Over 4 Years and The Overlap with DAPSA and MDA Disease Activity Targets [Abstract]. Ann Rheum Dis. 2019;78:1836-1837	Outcomes not relevant to scope
Coates LC, van der Heijde D, Kristensen LE, et al. Achievement of Remission is Associated with Improvement in Functionality in Certolizumab Pegol-Treated Patients with Psoriatic Arthritis, Irrespective of Pre-Existing Radiographic Structural Damage [Abstract]. Arthritis Rheumatol. 2020;72(Suppl 10)	Previously known information about certolizumab pegol related to efficacy
Yamazaki H, So R, Matsuoka K, et al. Certolizumab Pegol for Induction of Remission in Crohn's Disease. Cochrane Database Syst Rev. 2019 Aug; 2019(8):CD012893	Previously known information about certolizumab pegol related to efficacy

Citation	Decision
Tanaka Y, Atsumi T, Yamamoto K, et al. Certolizumab Pegol in Japanese Patients with Early Rheumatoid Arthritis: Disease Activity and Radiographic Progression across Rheumatoid Factor Quartiles (C-OPERA Study) [Abstract]. Int J Rheum Dis. 2020;23(Suppl 1), 254-255	Previously known information about certolizumab pegol related to efficacy
Saraux A, Flipo RM, Fagnani F, et al. Early Non-Response to Certolizumab Pegol in Rheumatoid Arthritis Predicts Failure to Achieve Low Disease Activity at 1 year: Data From a Prospective Observational study [Manuscript]. RMD Open. 2020;6(1)	Previously known information about certolizumab pegol related to efficacy
Saraux A, Combe B, Fagnani F, et al. Long-Term Clinical Outcomes in Patients with Rheumatoid Arthritis Treated with Certolizumab Pegol: Results from the French ECLAIR Study [Manuscript]. 2020 Sep 1;Online ahead of print	Previously known information about certolizumab pegol related to efficacy
Tanaka Y, Li Z, Inanc N, et al. Certolizumab pegol in patients with rheumatoid arthritis: pooled efficacy analysis of phase 3 clinical trials across baseline rheumatoid factor quartiles [Abstract]. Ann Rheum Dis;2020;79(Suppl 1):271-272	Previously known information about certolizumab pegol related to efficacy
Paul S, Marotte H, Kavanaugh A, et al. Exposure-Response Relationship of Certolizumab Pegol and Achievement of Low Disease Activity and Remission in Patients with Rheumatoid Arthritis [Manuscript]. ClinTransl Sci. 2020; 13(4):743–751	Previously known information about certolizumab pegol related to efficacy
Burmester G, Nüsslein H, von Hinüber U, Jet al. Effectiveness and Safety of Anti-Tumor Necrosis Factor Therapy with Certolizumab Pegol Observed in Real-life Rheumatoid Arthritis Patients in Germany: Results from the Non-Interventional FasT Study [Manuscript]. Clin Exper Rheumatol. 2019 Mar;37(5).	Previously known information about certolizumab pegol related to efficacy
Coates L, Merola JF, Kavanagh A, et al. Achievement of Very Low Disease Activity and Remission Treatment Targets is Associated with Reduced Radiographic Progression in Patients with Psoriatic Arthritis Treated with Certolizumab Pegol [Poster]. Ann Rheum Dis. 2020;79(Suppl 1):758-759.	Previously known information about certolizumab pegol related to efficacy
Gottlieb AB, Gisondi P, Eells J, et al. Durability of Response in Patients with Psoriatic Arthritis Treated with Certolizumab Pegol over 216 Weeks: Post-Hoc Analyses from the RAPID-PsA Study [Poster]., SKIN The Journal of Cutaneous Medicine. 2020;4(1):S2	Previously known information about certolizumab pegol related to efficacy
Pope J, Rampakakis E, Vaillancourt J, et al. An Open-Label Randomized Controlled Trial of DMARD Withdrawal in RA Patients Achieving Therapeutic Response with Certolizumab Pegol Combined with DMARDs [Manuscript]. Rheumatology (Oxford). 2019;59(7):1522-1528.	Previously known information about certolizumab pegol related to efficacy
van de Kerkhof P, Pinter A, Boehnlein M, et al. Efficacy of Certolizumab Pegol for Psoriasis of the Head and Neck in Two Phase 3 Clinical Trials: CIMPASI-1 and CIMPASI-2 [Poster].SKIN The Journal of Cutaneous Medicine. 2019;3(S40)	Previously known information about certolizumab pegol related to efficacy
Warren RB, Gordon K, Gottlieb AB, et al. Efficacy of Continued Certolizumab Pegol Treatment in Patients with Plaque Psoriasis Showing a Response Between PASI 75 and 90 Following the First 16 Weeks of Treatment [Poster]. No citation available.	Previously known information about certolizumab pegol related to efficacy
Gordon K, Warren RB, Gottlieb AB, et al. Durable Efficacy of Certolizumab Pegol Dosed at 400 mg Every Two Weeks Over 128 Weeks in Patients with Plaque Psoriasis Enrolled in Three Phase 3 Trials (CIMPASI-1, CIMPASI2 and CIMPACT) [Poster]. SKIN The Journal of Cutaneous Medicine. 2020;4(5):s45	Previously known information about certolizumab pegol related to efficacy
Merola JF, Reich K, Boehnlein M, et al. Physician Global Assessment and Body Surface Area Composite Tool Response in Patients with Plaque Psoriasis after 16 and 48 Weeks' Certolizumab Pegol Treatment [Abstract]. J Clin Aesthet Dermatol. 2019;12(5):S28 ..	Previously known information about certolizumab pegol related to efficacy



Citation	Decision
Blauvelt A, Warren RB, Reich K,. Durable Improvement in Patient-Reported Outcomes (PROs) across DLQI Subdomains Over 48 Weeks in Chronic Plaque Psoriasis Patients Treated with Certolizumab Pegol in Two Phase 3 Trials (CIMPASI-1 and CIMPASI-2) [Abstract]. SKIN The Journal of Cutaneous Medicine. 2019 Mar 11;3(2):175.	Previously known information about certolizumab pegol related to efficacy
Augustin M, Lebwohl M, Piguat V, et al. Efficacy of Continued Certolizumab Pegol Treatment in Patients Who Inadequately Respond in the First 16 Weeks: Results from the CIMPACT Trial [Abstract]. J Eur Acad Dermatol Venereol.2019;33(S3):45-85(	Previously known information about certolizumab pegol related to efficacy
Gottlieb AB, Thaçi D, Leonardi C, et al. Nail Outcome Improvements with Certolizumab Pegol in Moderate to Severe Plaque Psoriasis: Results from Phase 3 Trials [Abstract]. SKIN The Journal of Cutaneous Medicine. 2019;3(S38) .	Previously known information about certolizumab pegol related to efficacy
Blauvelt A, Reich K, Lebwohl M, et al. Certolizumab pegol for the treatment of patients with moderate-to-severe chronic plaque psoriasis: pooled analysis of week 16 data from three randomized controlled trials [Manuscript]. J Eur Acad Dermatol Venereol. 2019 Mar;33(3):546–552.	Previously known information about certolizumab pegol related to efficacy
Blauvelt A, Brock F, Rosario-Jansen T, et al. Efficacy of certolizumab pegol in patients with psoriasis and skin of color: pooled data from four randomized, placebo-controlled phase 2/3 trials [Poster]. No citation available.	Previously known information about certolizumab pegol related to efficacy
Lebwohl M, Piguat V, Sofen H, et al. The Efficacy of Certolizumab Pegol Re-Treatment on Plaque Psoriasis Following a Blinded Treatment Break: Results from the CIMPACT Trial [Abstract]. SKIN The Journal of Cutaneous Medicine. 2019 Mar 11;3(2):174.	Previously known information about certolizumab pegol related to efficacy
Landewe RBM, van der Heijde D, Dougados M, et al. Does Gender, Age or Subpopulation Influence the Maintenance of Clinical Remission in Axial Spondyloarthritis Following Certolizumab Pegol Dose Reduction? [Poster]. Ann Rheum Dis. 2020;79(Suppl 1):66-67.	Previously known information about certolizumab pegol related to efficacy
van der Horst-Bruinsma I, van Bentum R, Verbraak FD, et al. Reduction of Anterior Uveitis Flares in Patients with Axial Spondyloarthritis Following 1 Year of Treatment with Certolizumab Pegol: 48-Week Interim Results from a 96-Week Open-Label Study [Oral Presentation]. Arthritis Rheumatol. 2019;71(Suppl 10).	Previously known information about certolizumab pegol related to efficacy
Bykerk V, Gottlieb AB, Reich K, et al. Durability of certolizumab pegol in patients with rheumatoid arthritis or psoriasis over three years: an analysis of pooled clinical trial data [Abstract] Ann Rheum Dis. 2020;79(Suppl 1):621	Previously known information about certolizumab pegol related to efficacy
Schenker H, Rech J, Tascilar K, et al. Central Nervous System Pain Response and Components of Disease Activity in RA Patients After Treatment with Certolizumab or Placebo: A Post-Hoc Analysis from the PRECEPRA Trial [Abstract]. Ann Rheum Dis. 2020;79(Suppl 1):135-136	Previously known information about certolizumab pegol related to efficacy
Blauvelt A, Strober B, Langley R, et al. Safety of Certolizumab Pegol in Plaque Psoriasis: Pooled 96-Week Data from Three Phase 3, Multicenter, Randomized, Placebo-Controlled Studies (CIMPASI-1, CIMPASI-2 and CIMPACT) [Abstract]. SKIN The Journal of Cutaneous Medicine. 2019;3(S39).	Previously known information about certolizumab pegol related to safety
Curtis JR, Mariette X, Gaujoux-Viala C, et al. Long-term Safety of Certolizumab Pegol in Rheumatoid Arthritis, Axial Spondyloarthritis, Psoriatic Arthritis, Psoriasis, and Crohn's Disease: A Pooled Analysis of 11,317 Patients across Clinical Trials [Manuscript]. RMD Open. 2019 May 1;5(1):e000942	Previously known information about certolizumab pegol related to safety
Lau CS, Chen YH, Lim K, et al. Tuberculosis and Viral Hepatitis in Patients Treated with Certolizumab Pegol in Asia-Pacific Countries and Worldwide:	Previously known information about certolizumab pegol related to safety



Citation	Decision
Real-World and Clinical Trial Data [Manuscript]. Clin Rheumatol. 2020;40:867-875	
Baraliakos X, Witte T, De Clerck L, et al. Effectiveness and Safety of 12-Month Certolizumab Pegol Treatment for Axial Spondyloarthritis in Real-World Clinical Practice in Europe [Manuscript]. Rheumatology (Oxford). 2021 Jan 5;60(1):113-124	Study published outside of the timeframe of our review
Asahina A, Umezawa Y, Sakurai S, et al. Efficacy and Safety of Certolizumab Pegol in the Treatment of Japanese Patients With Psoriasis: Interim Week 24 Analyses from a 52-Week Phase 2/3, Randomised, Placebo-Controlled Study [Poster]. Presented at the 28th European Academy of Dermatology and Venerology (EADV) Congress in Madrid, Spain Oct. 09-13, 2019. .	Study published outside of the timeframe of our review
Gordon K, Warren RB, Gottlieb AB, et al. Long-Term Efficacy of Certolizumab Pegol Dosed at 400 mg Every Two Weeks in Patients with Plaque Psoriasis: Pooled 128-Week Data from Two Phase 3 Trials (CIMPASI-1 and CIMPASI-2) [Manuscript]. Br J Dermatol. 2021 Apr;184(4):652-662	Study published outside of the timeframe of our review
Thaçi D, Blauvelt A, Reich K, et al. Long-term improvements in health-related quality of life of patients with moderate to severe plaque psoriasis treated with certolizumab pegol: Results from the CIMPASI-1 and CIMPASI-2 phase 3 trials [Poster]. SKIN The Journal of Cutaneous Medicine. 2021;5(1), s20	Study published outside of the timeframe of our review
Blauvelt A, Warren RB, et al. Durability of DLQI Improvements Among Patients with Moderate to Severe Plaque Psoriasis Treated with Certolizumab Pegol: Three-Year Results from Two Phase 3 Trials (CIMPASI-1 and CIMPASI-2) [Poster]. SKIN The Journal of Cutaneous Medicine. 2021;5(1), s19	Study published outside of the timeframe of our review

\*One duplicate reference identified and not included.

# Appendix I. Entresto®

**Appendix Table I1. References Submitted by Novartis**

Citation	Decision
Yancy CW, Hernandez AF, Bonow RO. The use of sacubitril/valsartan for hospitalized heart failure—why do we care about cost and value? [published online ahead of print August 12, 2020]. JAMA Cardiol. 2020. doi:10.1001/jamacardio.2020.3108.	Editorial
Mc Causland FR, Lefkowitz M, Claggett B, et al. Angiotensin-Neprilysin Inhibition and Renal Outcomes in Heart Failure. Circulation. 2020 Sep 29;142(Supplement 3):A17063.	Low-quality evidence
Gaziano TA, Fonarow GC, Velazquez EJ, Morrow DA, Braunwald E, Solomon SD. Cost-effectiveness of sacubitril-valsartan in hospitalized patients who have heart failure with reduced ejection fraction [published online ahead of print August 12, 2020]. JAMA Cardiol. 2020. doi:10.1001/jamacardio.2020.2822	Low-quality evidence
Shafrin J, Aliyev ER, Brauer M, et al. Alternative payment models and innovation: a case study of US health system adoption of a sacubitril/valsartan to treat acute decompensated heart failure. J Med Econ. 2020 Dec;23(12):1450-1460.	Low-quality evidence
Effects of the Angiotensin-Receptor Neprilysin Inhibitor on Cardiac Reverse Remodeling: Meta-Analysis Wang et al. JAHA 2019	Outcomes not relevant to our scope
Desai AS, Solomon SD, Shah AM, et al. Effect of sacubitril-valsartan vs enalapril on aortic stiffness in patients with heart failure and reduced ejection fraction (EVALUATE-HF). JAMA. 2019;322(11):1077-1084.	Outcomes not relevant to our scope
Januzzi JL Jr, Prescott MF, Butler J, et al. Association of change in N-terminal pro-B-type natriuretic peptide following initiation of sacubitril-valsartan treatment with cardiac structure and function in patients with heart failure with reduced ejection fraction (PROVE-HF). JAMA. 2019;322(11):1-11.	Outcomes not relevant to our scope
Wachter R, Senni M, Belohlavek J, et al. Initiation of sacubitril/valsartan in haemodynamically stabilised heart failure patients in hospital or early after discharge: primary results of the randomised TRANSITION study. Eur J Heart Fail. 2019;21(8):998-1007.	Previously known information about sacubitril/valsartan related to efficacy
Albert NM, Swindle JP, Buysman EK, Chang C. Lower hospitalization and healthcare costs with sacubitril/valsartan versus angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker in a retrospective analysis of patients with heart failure. J Am Heart Assoc. 2019;8(9):e011089.	Previously known information about sacubitril/valsartan related to efficacy
Greene SJ, Lippmann SJ, Mentz RJ, et al. Clinical effectiveness of sacubitril/valsartan among patients hospitalized for heart failure with reduced ejection fraction. J Card Fail. 2019;25(11):P937.	Previously known information about sacubitril/valsartan related to efficacy
Khariton Y, Fonarow GC, Arnold SV, et al. Association between sacubitril/valsartan initiation and health status outcomes in heart failure with reduced ejection fraction. JACC Heart Fail. 2019;7(11):933-941.	Previously known information about sacubitril/valsartan related to efficacy
Tan NY, Sangaralingham LR, Sangaralingham SJ, Yao X, Shah ND, Dunlay SM. Comparative effectiveness of sacubitril-valsartan versus ACE/ARB therapy in heart failure with reduced ejection fraction. JACC Heart Fail. 2020;8(1):43-54.	Previously known information about sacubitril/valsartan related to efficacy
Spannella F, Giulietti F, Filippini A, et al. Effect of sacubitril/valsartan on renal function: a systematic review and meta-analysis of randomized controlled trials. ESC Heart Fail. 2020 Sep 22;7(6):3487–96.	Previously known information about sacubitril/valsartan related to efficacy

## Appendix J. Krystexxa®

**Appendix Table J1. References Submitted by Horizon Therapeutics**

Citation	Decision
Botson J and Peterson J. Pretreatment and Coadministration with methotrexate improved durability of pegloticase response. Journal of Clin Rheum. 2020. [Epub ahead of print].	Intervention/comparison not relevant to scope
Rainey H, Baraf H, Yeo AE and Lipsky PE. Companion immunosuppression with azathioprine increases the frequency of persistent responsiveness to pegloticase in patients with chronic refractory gout. Poster presented at the American College of Rheumatology Convergence; November 5 - 9, 2020; Virtual meeting.	Intervention/comparison not relevant to scope
Baraf H, Rainey H, Lipsky P. The impact of azathioprine on the frequency of persistent responsiveness to pegloticase in patients with chronic refractory gout [abstract]. Art hr . Rheumatol. 2020;72(suppl 10).	Intervention/comparison not relevant to scope
Khanna P, Khanna D, Cutter G 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. Oral presentation at the American College of Rheumatology Convergence; November 5 - 9, 2020; Virtual meeting.	Intervention/comparison not relevant to scope
Botson J, Peloso P, Obermeyer Ket 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. Poster presented at the American College of Rheumatology Convergence; November 5 - 9, 2020; Virtual meeting	Intervention/comparison not relevant to scope
Albert JA, Hosey T and LaMoreaux B. Increased Efficacy and Tolerability of pegloticase in patients with uncontrolled gout co-treated with methotrexate: A retrospective study. Rheumatol Ther. 2020;7(3):639-648.	Intervention/comparison not relevant to scope
Johnson RJ, Choi HK, Yeo AE and Lipsky PE. Pegloticase treatment significantly decreases blood pressure in patients with chronic gout. Hypertension. 2019;74(1):95- 101.	Outcomes not relevant to our scope
Bleyer AJ, Zhang Y, Kshirsagar OS, Marder BA and LaMoreaux 8. A USRDS Database study on the use of pegloticase in patients undergoing dialysis. Poster presentation at Kidney Week (American Society of Nephrology); October 20 - 25, 2020; Virtual meeting.	Low-quality evidence
Soloman N, Amin M, Cox K et al. Management of gout with pegloticase; real-world utilization and outcomes from Trio Health and the American Rheumatology Network (ARN). Poster presented at the American College of Rheumatology Convergence; November 5 - 9, 2020; Virtual meeting.	Outcomes not relevant to our scope
Schlesinger N, Yeo A and Lipsky P. Treatment with pegloticase improves hepatic fibrosis estimated by fibrosis-4 index in subjects with chronic refractory gout. Poster presented at the EULAR Annual European Congress of Rheumatology; June 3 - 6, 2020; Virtual meeting.	Outcomes not relevant to our scope
Edwards NL, Singh JA, Troum O, Yeo AE and Lipsky PE. Characterization of patients with chronic refractory gout who do and do not have clinically apparent tophi and their response to pegloticase. Rheumatology (Oxford). 2019;kez017 [Epub ahead of print].	Outcomes not relevant to our scope

Citation	Decision
Song V, Xin V, Weinblatt M et al. Pharmacokinetics of pegloticase and methotrexate polyglutamate(s) in patients with uncontrolled gout receiving pegloticase and co treatment of methotrexate. Poster presented at the American College of Rheumatology Convergence; November 5 - 9, 2020; Virtual meeting.	Outcomes not relevant to our scope
LaMoreaux B, Botson J, Francis-Sedlak M et al. Trends in Immunomodulation/pegloticase co-therapy from 2015 - 2019: A Claims Database Study. Poster presented at the American College of Rheumatology Convergence; November 5 - 9, 2020; Virtual meeting.	Outcomes not relevant to our scope
Pillinger MH, Fields TR, Yeo AE and Lipsky PE. Dissociation between clinical benefit and persistent urate lowering in patients with chronic refractory gout treated with pegloticase. J Rheumatol. 2020;47(4):605-612.	Previously known information about Krystexxa related to efficacy
Abdellatif A, Lin Z, Peloso P et al. Pegloticase for uncontrolled gout in kidney transplant recipients: Early data report of a multicenter, open-label efficacy and safety study. Oral presentation at Kidney Week (American Society of Nephrology); October 20 - 25, 2020; Virtual meeting.	Indication accounts for less than 10% of use
Botson J, Tesser JRP, Bennett R et al. Pegloticase in combination with methotrexate in patients with uncontrolled gout: a multicenter, open-label study (MIRROR). The Journal of Rheumatology. 2021;48(5):767-774. Epub 2020 Sep 15*.	Low-quality evidence
Masri K, Winterling K and LaMoreaux B. Leflunomide co-therapy with pegloticase in uncontrolled gout. Poster presented at the EULAR Annual European Congress of Rheumatology; June 3 - 6, 2020; Virtual meeting.	Study published outside of the timeframe of our review

\*Study published outside of the timeframe of our review. However, we reviewed because it was e-published on September 15, 2020, within the 2019-2020 Evidence Review Period.

## Appendix K. Fanapt®

---

**Appendix Table K1. References Submitted by Vanda Pharmaceuticals**

Citation	Decision
N/A	N/A

## Appendix L. Emflaza®

---

**Appendix Table L1. References Identified by ICER Systematic Literature Review**

Citation	Decision
McDonald CM, Sajeev G, Yao Z, et al. Deflazacort vs prednisone treatment for Duchenne muscular dystrophy: A meta-analysis of disease progression rates in recent multicenter clinical trials. <i>Muscle Nerve</i> . 2020;61(1):26-35.	Previously known information about deflazacort related to efficacy
Marden JR, Freimark J, Yao Z, Signorovitch J, Tian C, Wong BL. Real-world outcomes of long-term prednisone and deflazacort use in patients with Duchenne muscular dystrophy: experience at a single, large care center. <i>J Comp Eff Res</i> . 2020;9(3):177-189	Previously known information about deflazacort related to efficacy
McDonald CM, Henricson EK, Abresch RT, et al. Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study. <i>Lancet</i> . 2018;391(10119):451-461.	Study published outside of the timeframe of our review
Marden J, Santos C, Pfister B, Able R, Lane H, Somma M, Zhao J, Signorovitch J, Parsons J, Apkon S. Steroid Switching in the Treatment of Dystrophinopathies in the US: a Nationwide Chart Review of Patient Characteristics and Clinical Outcomes. Muscular Dystrophy Association Conference 2021.	Study published outside of the timeframe of our review

## Appendix M. ICER Systematic Literature Review

**Appendix Table M1. ICER Systematic Literature Review Results**

Drug	Search Yield	References Screened in Full-Text	New Evidence Identified
Humira®	155	31	0
Promacta®	16	5	0
Tysabri®	35	2	0
Xifaxan®	19	12	0
Trokendi XR®	96	5	0
Venclexta®	57	16	4
Lupron Depot®	47	8	0
Cimzia®	65	15	3
Entresto®	41	16	1
Krystexxa®	5	0	0
Fanapt®	4	0	0
Emflaza®	8	0	0

Evidence identified for Venclexta®, Cimzia®, and Entresto® overlaps with references submitted by their respective manufacturers.

**Appendix Table M2. Sample Search Strategy in Embase**

1	'eltrombopag'/exp OR 'promacta':ti,ab OR 'eltrombopag':ti,ab
2	'randomized controlled trial'/exp OR 'controlled clinical trial'/exp
3	#1 AND #2
4	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
5	3 NOT 4
6	#5 and [English]/lim
7	#6 NOT ('case report'/de OR 'human tissue'/de OR 'nonhuman'/de OR 'practice guideline'/de OR 'questionnaire'/de OR 'chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
8	#7 AND [2019-2020]/PY

# Appendix N. ICER Responses to Manufacturer Comments

## General Evidence Response

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

### 1. New Clinical Evidence

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



2. Real-World Evidence (RWE)
  - a. ICER applies the same evidentiary standards to RWE that it applies to all other forms of evidence and is happy to consider RWE as part of the UPI Report.
  - b. High-quality RWE can be particularly valuable in assessing effectiveness of therapies and issues around adherence.
3. Quality of Observational Evidence
  - a. As noted in the [UPI Protocol](#), 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
<b>AbbVie</b>		
1.	<p>Value assessments provide an incomplete answer to whether a given treatment offers value. AbbVie believes that value assessment frameworks that are informed by the totality of available clinical, economic, and humanistic evidence can help to inform the value determination made by healthcare decision makers and policymakers but are not the sole determinant of value. That said, 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 in part: "...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 provide information in a useful timeframe for the public and policymakers. Therefore, UPI reports are not intended to determine whether a price increase for a drug is fully justified by new clinical evidence or meets an ICER health-benefit based price benchmark." Further, as stated in the ISPOR Special Task Force Report on US Value Assessment Framework, "...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." Despite ICER's own recognition that it lacks the capacity to perform full economic analyses that would be necessary to arrive at the conclusions in this report, the UPI report is published without adequate context or clarity for why ICER feels justified in making such inferences. In doing so, ICER ignores the potential impact such conclusions could have on patient access if the report is utilized without the complete context and research.</p>	<p>The ICER UPI Report is not a value assessment. Policymakers and the public in general can decide for themselves whether they feel that when the most expensive drugs in the US raise prices there should be new high-quality evidence of benefits not previously known.</p>
2.	<p>AbbVie submitted a total of 140 references as evidentiary support for the updated safety and clinical effectiveness of Venclexta, Lupron, and Humira. ICER concluded that only Venclexta had new clinical evidence of moderate to high quality in demonstrating substantial benefit for patients. We question ICER's evaluation and interpretation of the submitted evidence for Lupron and Humira and bring to your attention the incomplete and misleading valuation caused by ICER's protocol methodology.</p> <ul style="list-style-type: none"> <li>Lupron Depot was granted a label update in 2019 (during the UPI protocol assessment period of January 2019-December 2020) stating "In patients treated with GnRH analogues for prostate cancer, treatment is usually continued upon development of non-metastatic and metastatic castration-resistant prostate cancer." This was based on the use of Androgen Deprivation Therapy (ADT) like Lupron as</li> </ul>	<p>Please see GER 1c, 5b, 3b.</p>

#	Comment	Response/Integration
	<p>backbone therapy in pivotal trials of apalutamide (SPARTAN) and enzalutamide (PROSPER) for prostate cancer. ICER stated that there was no evidence that Lupron was the background ADT in the PROSPER trial and concluded that Lupron had unsupported new clinical evidence. However, through AbbVie's discussion with the FDA, Lupron is the only GnRH agonist to have received the new label language update and confirmed its important role in helping cancer patients.</p> <ul style="list-style-type: none"> <li>• In limiting the assessment to indications representing greater than 10 percent use, ICER excluded HUMIRA's clinical and economic evidence in smaller patient populations, including rare conditions (i.e., hidradenitis suppurativa and uveitis) and pediatric populations (i.e., pediatric ulcerative colitis for which the FDA expanded HUMIRA use in 2020) that reflect our commitment to innovation and improvement in net health benefit to underserved populations with high unmet needs.</li> <li>• Citing Chambers, 2019 as a well-performed observational study conducted to address the safety of HUMIRA in pregnancy and yet concluding it did not meet the criteria of moderate to high quality evidence raises into question the subjective nature of ICER's rating of new quality evidence and additional net health benefit. Dismissing a valid study without an objective basis raises significant questions as to ICER's approach.</li> </ul>	
3.	<p>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 Part D and Medicaid ultimately pay for drugs. Unlike list prices, data on net prices are not readily available. SSR Health is a database that estimates net drug prices of drugs manufactured by publicly traded companies by dividing overall manufacturer revenues for a given drug (as reported to the US Securities and Exchange Commission and in other industry reports) by the total number of units dispensed (according to data from Symphony Health). SSR Health calculations of net drug prices are estimates and limited by uncertainty and quality along the drug supply chain.</p>	<p>Data on net prices are readily available to the manufacturer. Many manufacturers submitted data on net prices for this UPI Report, and AbbVie was given the opportunity to make such submissions.</p>
<b>Bausch Health</b>		
1.	<p>First, we wish to highlight that ICER initially miscalculated our net sales revenue. We requested that ICER correct this error, and after providing ICER with additional, non-public details, ICER cut its estimate by nearly half of net revenue increase due to price increases. Bausch Health never received an explanation process that led to the original</p>	<p>The UPI process includes the opportunity for manufacturers to submit corrected data on net sales.</p> <p>The <a href="#">UPI Protocol</a> looks at the increase in medical CPI when assessing WAC increases, not net increases.</p>

#	Comment	Response/Integration
	<p>error, eroding our ability to supply the necessary data to ensure accuracy.</p> <p>We also question the usefulness of including XIFAXAN® in the report at all. ICER estimates that the net price increase on XIFAXAN® was 3.0%, a figure that is substantially below ICER's estimate of medical inflation. When adjusted for inflation, the price of XIFAXAN® fell, making the inclusion of the medicine an unusual choice in a report nominally about price increases.</p>	
2.	<p>Secondly, ICER inappropriately excluded research from its review. Last year, in the 2020 UPI assessment, Bausch Health provided two pieces of cost-effectiveness evidence (Bozkaya D, 2014; Jesudian AB, 2020) to support the value of XIFAXAN®. At that time, ICER excluded both publications with the same rationale: "Study published outside of the timeframe of our review," implying that the Bozkaya paper was too old to have had an impact on our pricing decisions and that the work by Jesudian AB was too recent. So, we were surprised when – after re-submitting the Jesudian AB publication for this year's review – ICER again refused to consider it, despite the study's relevance and publication during the ICER "Evidence Review Period" of January 2019 – December 2020.</p> <p>In the 2021 UPI preliminary assessment of XIFAXAN® (dated September 13, 2021), Jesudian AB was excluded with the following reason provided by ICER: "Previously known information about rifaximin related to cost." We dispute this characterization and hold that ICER's exclusion of Jesudian AB is unjustified.</p> <p>Jesudian AB featured a cost-effectiveness analysis (CEA) model amongst patients with overt hepatic encephalopathy (HE), comparing rifaximin 550 mg twice daily with lactulose monotherapy from a U.S. third-party perspective over a lifetime horizon. The Jesudian AB study used updated and proximate model inputs such as life expectancy after liver transplantation from UNOS 2016 report. This UNOS 2016 update includes meaningful changes in estimates of the life expectancy after liver transplantation and has a major impact on cost-effectiveness results and therefore the value delivered by XIFAXAN®.</p> <p>Jesudian AB also uses updated health state utilities, derived from Guest JF, 2014 which uses the time trade-off and standard gamble method to estimate utilities specific to the HE population, and the research used more current cost data. The Jesudian AB study shows that the incremental cost-effectiveness ratio per quality adjusted</p>	<p>We agree that Jesudian does potentially provide new information related to cost and we have reviewed it. Economic models rarely provide high or moderate-quality evidence by GRADE criteria, and that matches with our conclusion about Jesudian. As an example, the model in Jesudian assumes mortality benefits based on a single-arm, open-label study. Mortality is clearly central to the modeling and yet the evidence for effects on mortality is of low (or very low) quality. Thus, we conclude that Jesudian does not provide high or moderate-quality evidence of a substantial benefit that was not previously known.</p>

#	Comment	Response/Integration
	<p>life years gained (in 2018 dollars) for rifaximin + lactulose vs. lactulose monotherapy is \$29,161, nearly 10% higher than previous estimates and still well within common accepted willingness-to-pay thresholds.</p> <p>The publication year (2020) of Jesudian AB not only falls in the ICER 2021 Review Period but is also a key building block of the CEA model (i.e., model inputs and CEA estimates [2018 \$]), reflecting the most recent data available to the authors for their CEA analysis and publication. This study provides evidence that supports and augments the value of XIFAXAN®.</p>	
<b>Biogen</b>		
1.	<p>Biogen provided 23 references relating to TYSABRI that were published in 2019 and 2020. ICER excluded all of these references in its assessment. Additionally, ICER did not conduct a search for additional new evidence. In addition to independent publications, Biogen has sponsored research that resulted in the publication of over 15 articles and over 70 presentations at various Neurology congresses in 2019-2020.</p> <p>Biogen believes that all of the references published in 2019-2020 consistently demonstrate TYSABRI's long-term efficacy and safety, its comparative effectiveness, and its significant impact on quality of life and other patient-reported outcomes (PROs) for patients with MS. Biogen respectfully disagrees with the exclusion of these studies from ICER's assessment as they provide important new and confirmatory clinical information on TYSABRI.</p>	Please see GER 1a, 1b, 5a.
2.	<p>While observational studies do not always merit a similar quality grade to that of randomized clinical trials (RCTs), it is disappointing that all of the observational studies for TYSABRI that Biogen submitted for this assessment have been excluded in this report as they provide valuable and important data and evidence to inform clinical care for people living with MS. It is mentioned in the GRADE guidelines that rigorous observational trials can provide stronger evidence than uncontrolled case series and that if the observational studies have special strengths, they should be considered high quality evidence in the evaluation. The study designs and limitations within the STRIVE, TYGRIS and TOP observational studies provided as publication support are representative of real-world populations on TYSABRI treatment and in which the endpoints are unique to the study populations. STRIVE provides information regarding long-term use of TYSABRI in a JCV-antibody negative population; TYGRIS was designed to capture long-term safety data in clinical practice; and TOP, one of the longest ongoing analyses of MS patients on TYSABRI therapy, has recently been</p>	Please see GER 1b, 3b.

#	Comment	Response/Integration
	<p>extended to include up to 15 years of experience. Excluding these studies dismisses a large volume of previously unpublished, peer-reviewed, scientific evidence, often for different patient subgroups than what was observed in the clinical trials, as well as longer follow-up durations and different data sources, and/or countries. Furthermore, these studies consistently show that TYSABRI efficacy and safety is similar to what has been seen in the pivotal trials even for periods of over 10 years.</p>	
<b>Horizon Therapeutics</b>		
1.	<p>Horizon submitted 17 studies published from 2019 to 2020 that demonstrate the clinical and economic value of KRYSTEXXA. ICER excluded these publications based on a range of justifications, including “intervention/comparison not relevant to scope,” “outcomes not relevant to scope,” “previously known information,” “indication accounts for less than 10% of use,” “study published outside of the timeframe of our review,” and “low quality evidence.” ICER’s exclusion of key scientific evidence that has already transformed the standard of care for uncontrolled gout compromises ICER’s ability to comprehensively and accurately assess the value of a product like KRYSTEXXA to patients, physicians, and payers.</p>	Please see GER 1a, 1b, 5b.
2.	<p>Horizon submitted 12 publications related to a series of studies on the use of immunomodulation (immune-modifying therapy) with KRYSTEXXA. Consistent with ICER’s UPI Protocol, these studies benefitted the treatment landscape for uncontrolled gout, generating new evidence beyond “what was previously generally believed about a therapy (whether its clinical or economic effects).” While KRYSTEXXA demonstrated rapid reduction in serum uric acid (sUA) level for people with uncontrolled gout in the clinical trials that were used as part of FDA approval, as with many biologic therapies, some people developed anti-drug antibodies (ADAs). Horizon engaged the clinical community to evaluate ways to improve effectiveness in these patients and invested significantly in clinical development programs to improve the response rate of 42% from the initial clinical trial.</p> <p>ICER’s decision to exclude all 12 of Horizon’s peer-reviewed immunomodulation publications from consideration in the UPI Report – generally on the basis that they involve an “intervention/comparison not relevant to scope” or “outcomes not relevant to scope” – is inconsistent with the value and significance of these studies. As a threshold matter, ICER has not adequately defined these terms, failing to provide sufficient criteria or description of studies that ICER would consider relevant to scope. The lack of such basic transparency undermines the credibility of ICER’s justifications for such exclusions.</p>	Please see GER 1c.

#	Comment	Response/Integration
	Substantively, it is difficult to understand how studies demonstrating improved efficacy and safety of KRYSTEXXA via concomitant use of immunomodulatory agents could possibly 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 physician community.	
3.	Horizon also submitted five publications reflecting development efforts to help clinicians understand the benefits of KRYSTEXXA among patients with comorbidities. Uncontrolled gout patients are known to have specific comorbidities including hypertension, dyslipidemia, chronic kidney disease, diabetes, coronary artery disease and cardiac failure, which add complexity to their management and increase their morbidity, mortality, and health care utilization. Horizon's development efforts with respect to these comorbidities contributes meaningful progress toward understanding KRYSTEXXA treatment across diverse and complex patient populations, and similarly should be considered meaningful new evidence supporting the value of KRYSTEXXA.	Please see GER 1a, 1b.
<b>Novartis</b>		
1.	<p>Per the 2019 guideline from the American Society of Hematology, persistent ITP is defined as ITP duration of three-12 months. Novartis received approval to modify the ITP indication statement to add "persistent" to remain consistent with the patient population enrolled in the registration clinical studies with adult and pediatric ITP, allowing patients to start on eltrombopag three months after ITP diagnosis and 1L treatment failure.</p> <p>In the past, ITP was categorized based on the length of time from initial diagnosis into 'acute' ITP that lasted for up to six months from initial diagnosis and 'chronic' ITP that lasted beyond six months from initial diagnosis. The International Working Group (IWG) released updated guidelines in 2009 (Rodeghiero et al. 2009), in which ITP was divided into 'newly diagnosed' ITP (lasting up to 3 months from diagnosis), 'persistent' ITP (lasting between three and 12 months from diagnosis) and 'chronic' ITP (lasting more than 12 months from diagnosis). This classification was recently reaffirmed by the American Society of Hematology (ASH), which suggests use of thrombopoietin receptor agonists (TPO-RA) as a treatment option in persistent ITP (lasting ≥3 months) patients who are corticosteroid-dependent or unresponsive to corticosteroids to achieve durable responses (Neunert et al. 2019).</p>	Please see GER 1a, 1b.



#	Comment	Response/Integration
	Study 773B randomized 114 patients (2:1) to eltrombopag 50 mg or placebo. Of 60 patients with documented time since diagnosis, approximately 17% met the definition of persistent ITP. Study 773A randomized 117 patients (1:1:1:1) among placebo or 1 of 3 dose regimens of eltrombopag, 30 mg, 50 mg, or 75 mg each administered daily. Of 51 patients with documented time since diagnosis, approximately 14% met the definition of persistent ITP.	
2.	<p>New observational comparative, prospective, retrospective, and case studies have shown that eltrombopag improves platelet counts, lowers the risk of bleeding related events, thromboembolic events, and lowers risk of long-term complications (e.g., pneumonia, septicemia). Specifically, new evidence proves that eltrombopag is effective and efficacious across a range of patient populations including: (i) second-line (2L) adult patients with chronic immune thrombocytopenia (cITP); (ii) elderly patients with primary or secondary ITP, (iii) and for patient populations outside the US.</p> <p>Recent studies show that eltrombopag can improve platelet counts, lower risks of bleeding related events, and lower risk of long-term complications for 2L treatment of cITP in adults.</p> <p>One study also demonstrates that eltrombopag has proven efficacy and effectiveness in elderly patients for the treatment of primary and secondary ITP.</p> <p>Global studies also demonstrated eltrombopag's short- and long-term effectiveness.</p>	Please see GER 1a, 1b.
3.	A systematic review and network meta-analysis (NMA) of treatment for adult persistent ITP found that romiplostim and eltrombopag had improved platelet response and platelet count compared to placebo. Twelve randomized controlled trials of 2L treatments of adult with persistent ITP were eligible for the NMA. Eltrombopag and romiplostin had the best platelet response; eltrombopag had a non-significant advantage [risk ratio (RR)=1.10 (95% CI: 0.46, 2.67)] against romiplostin. Both treatments were superior to rituximab and recombinant human thrombopoietin+rituximab with eltrombopag corresponding RRs of 4.56 (1.89, 10.96) and 4.18 (1.21, 14.49).	Please see GER 4a.
4.	In a meta-analysis that evaluated the efficacy and safety of eltrombopag in adults and children with ITP, researchers found safe and efficient use of eltrombopag in ITP versus placebo. The meta-analysis included 7 studies with a total of 765 patients (606 adults and 159 children). The number of patients needing rescue treatment and number of	Please see GER 1a, 1b.



#	Comment	Response/Integration
	bleeding incidents were reduced in the group that received eltrombopag versus placebo. The total number of adverse effects did not statistically differ between the two groups. Additionally, a prospective, multi-center Phase 2 trial of 51 patients found that eltrombopag remains a safe treatment option. Twenty-three patients (45%) reported a total of 51 AEs and 16 SAEs, with only 5 AEs considered treatment related. Eltrombopag was interrupted because of toxicity in three patients (6%). Further, a retrospective real-world study using the French CARMEN also found that 16.8% of patients experienced adverse drug reactions.	
5.	The ITP World Impact Survey (I-WISH), a cross-sectional survey of 1,507 patients that evaluated the impact of ITP on health-related quality of life, found that patients treated with anti-CD20 agents reported high overall satisfaction regarding control of their ITP for those receiving thrombopoietin receptor agonists (76%; n = 182/240). Additionally, 90% patients preferred orally administered ITP over an injection. The oral formulation may provide value during the COVID-19 pandemic as it may reduce the risk of transmission from having to visit an office to receive treatment and increased patient access when physician offices were closed during the COVID-19 pandemic.	This is a newly submitted reference. Therefore, we will not be reviewing it as it is long past the deadline stated in the UPI Protocol for evidence submission and evaluation.
6.	Cohort studies have shown that 3%-33% of patients with ITP may go into remission and maintain hemostatic platelet counts after tapering and discontinuing TPO-RAs. Based on this recent evidence, annual per patient payer cost is likely to fall as clinicians become aware that tapering and eventually discontinuing treatment is a feasible option for patients with stable response. A modified Delphi panel of US clinical experts concluded that TPO-RA can be tapered by decreasing the dose periodically to the minimum available dose but maintaining the time interval between doses. The Delphi Panel findings are supported by other studies which found that intermittent eltrombopag dosage in primary ITP provides similar safety and efficacy as daily dosing. A retrospective review in 508 adult patients treated with eltrombopag for primary ITP found that patients were able to maintain response after treatment discontinuation ( $\geq 6$ months) and long-term response after discontinuation ( $\geq 36$ months). Seventy-four patients (14.6%) successfully discontinued eltrombopag, and 38 patients (51.3%) maintained treatment-free response at 36 months. A retrospective analysis that assessed ITP newly diagnosed, non-splenectomized patients with ITP who received TPO-RAs, found that the overall response rate was 79.2%, while the discontinuation rate in all ITP patients were 41.6%. Another retrospective study found that the discontinuation rate for patients with a stable response was 40% in patients with newly	These are newly submitted references. Therefore, we will not be reviewing them as it is long past the deadline stated in the UPI Protocol for evidence submission and evaluation.

#	Comment	Response/Integration
	diagnosed and persistent ITP patients. In Italy, a study confirmed that responders were able to taper and discontinue use of TPO-RAs.	
7.	Results from a budget impact model (BIM) from the US private payer perspective show that the introduction of eltrombopag in 2L cITP is predicted to yield cost savings. The model has a 3-year time horizon and assumed a hypothetical 1-million member US private health plan. Over 3 years, total costs in the scenario without eltrombopag were \$5.63 million, whereas total costs in the scenario with eltrombopag were \$4.46 million. The model estimated the total budget impact, from the addition of eltrombopag to a health plan formulary for 2L cITP, to be an average of -\$1.18 million over the course of the 3-year time horizon. On a per patient basis, average savings were estimated to be -\$35,632 over the course of the 3-year time horizon.	This is a newly submitted reference. Therefore, we will not be reviewing it as it is long past the deadline stated in the UPI Protocol for evidence submission and evaluation. Furthermore, this reference is cited as “data on file.” We feel that if a manufacturer is planning to raise prices based on new evidence, that evidence should be available to the public.
8.	A cost-minimization analysis found that eltrombopag resulted in \$64,770 lower cost compared to romiplostim from a US health plan perspective. The base case used a commercial plan perspective, with average dosing of 51.5 mg/day for eltrombopag and 4.20 µg/kg/week for romiplostim; eltrombopag remained the less costly option for all plan types and assumptions. Based on a hypothetical commercial plan with 1 million members and an estimated 15 cITP patients receiving romiplostim, potential annual savings for switching all patients from romiplostim to eltrombopag was \$971,554 or \$0.08 per member per month.	This is a newly submitted reference. Therefore, we will not be reviewing it as it is long past the deadline stated in the UPI Protocol for evidence submission and evaluation.
9.	In addition to BIM, real-world data support the economic value of eltrombopag. A retrospective claims database study (2014-2017) (n=82) evaluating healthcare resource use and direct costs before and after eltrombopag use among patients with severe aplastic anemia showed significantly lower hospitalization, ER and outpatient visits following 6-month use of eltrombopag; with an overall mean reduction in total all-cause costs of \$29,391 (SD= \$137,770) due to substantial reduction in hospitalization costs and outpatient costs.	Please see GER 2b, 3b, 5a.
10.	A recent cost effectiveness analysis compared eltrombopag with romiplostim using a Markov model implemented over a lifetime horizon featuring clinically meaningful health states (on treatment, treatment discontinuation, mortality) using clinical trial data for health state transitions. The cost of drugs, routine care, bleeding episodes and adverse events were represented in the model. The total lifetime cost of eltrombopag treatment was estimated at \$1.58 million versus \$2.13 million for romiplostim. Eltrombopag therapy resulted in a gain of 17.58 LYs and 14.68 QALYs over a lifetime time	This is a newly submitted reference. Therefore, we will not be reviewing it as it is long past the deadline stated in the UPI Protocol for evidence submission and evaluation.

#	Comment	Response/Integration
	horizon, improvements of 0.06 and 0.01 compared with romiplostim. Eltrombopag was “dominant” in terms of both LYs and QALYs, as it was associated with lower cost and slightly greater benefit than romiplostim. In all probabilistic iterations, the total cost of eltrombopag treatment was lower than with romiplostim, primarily because of lower drug costs.	
<b>UCB</b>		
1.	<p>UCB has continued to invest in developing new clinical evidence for CIMZIA, which, as ICER concludes in its UPI report, supports CIMZIA’s pricing during ICER’s timeframe for review.</p> <p>Since CIMZIA was first approved, UCB has continued to generate evidence to discover the potential of CIMZIA for additional patient populations with high unmet need, including those suffering from nr-axSpA. nr-axSpA is a chronic inflammatory condition in which the immune system attacks healthy tissue in the spine and sacroiliac joints (which link the pelvis and the spine). Patients diagnosed with nr-axSpA are faced with significant disease burden, including chronic and often debilitating back pain, stiffness, and fatigue, and receive sub-optimal treatment. Based on results from the C-axSpAnd trial—a Phase III, multi-center, double-blind, placebo-controlled 52-week study in which patients treated with CIMZIA demonstrated major improvement over those given placebo—FDA granted approval of CIMZIA for the treatment of nr-axSpA in March 2019. With this label expansion, CIMZIA became the first FDA-approved treatment for nr-axSpA, and, to date, remains the only TNF inhibitor approved to treat nr-axSpA. UCB agrees with ICER’s characterization of the C-axSpAnd study as new, “high-quality evidence of a substantial benefit of treatment with [CIMZIA] for patients with axSpA” and its resultant conclusion that CIMZIA’s pricing was supported during the timeframe of ICER’s review.</p>	<p>To clarify, the UPI analysis does not examine whether the price for Cimzia is justified. This would require a full cost-effectiveness analysis, which was not performed. The UPI Report concluded that there was high-quality evidence of a benefit with Cimzia that was not previously known. Thus, Cimzia had a price increase with new evidence.</p>

Full-text manufacturer comments on our preliminary assessments are displayed on the following pages.

## Unsupported Price Increase Report 2021 Assessment

### AbbVie Response to Preliminary Assessment Report

October 12, 2021

AbbVie welcomes the opportunity to comment on ICER's Preliminary Unsupported Price Increase (UPI) assessments of Venclexta, Lupron, and Humira. In this assessment, ICER aims to review new evidence to evaluate the increase in price from 2019 to 2020.

**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.**

Value assessments provide an incomplete answer to whether a given treatment offers value.<sup>1</sup> AbbVie believes that value assessment frameworks that are informed by the totality of available clinical, economic, and humanistic evidence can help to inform the value determination made by healthcare decision makers and policymakers but are not the sole determinant of value. That said, 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 in part: "...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 provide information in a useful timeframe for the public and policymakers. Therefore, UPI reports are not intended to determine whether a price increase for a drug is fully justified by new clinical evidence or meets an ICER health-benefit based price benchmark."<sup>2</sup> Further, as stated in the ISPOR Special Task Force Report on US Value Assessment Framework, "...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"<sup>3</sup> Despite ICER's own recognition that it lacks the capacity to perform full economic analyses that would be necessary to arrive at the conclusions in this report, the UPI report is published without adequate context or clarity for why ICER feels justified in making such inferences. In doing so, ICER ignores the potential impact such conclusions could have on patient access if the report is utilized without the complete context and research.

**AbbVie believes the totality of evidence is necessary to help inform treatment and prescribing decisions by patients and healthcare providers as well as policy decisions made by payers.** Value assessments 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) is paramount to ensuring all appropriate therapies are accessible to patients and healthcare providers. Evaluating and understanding all available and relevant evidence together with patient experience not only offers the ability to advance society's

understanding of the medicines and the diseases they treat but also best demonstrates the holistic value of a medicine.

AbbVie submitted a total of 140 references as evidentiary support for the updated safety and clinical effectiveness of Venclexta, Lupron, and Humira. ICER concluded that only Venclexta had new clinical evidence of moderate to high quality in demonstrating substantial benefit for patients. We question ICER's evaluation and interpretation of the submitted evidence for Lupron and Humira and bring to your attention the incomplete and misleading valuation caused by ICER's protocol methodology.

- Lupron Depot was granted a label update in 2019 (during the UPI protocol assessment period of January 2019-December 2020) stating *"In patients treated with GnRH analogues for prostate cancer, treatment is usually continued upon development of non-metastatic and metastatic castration-resistant prostate cancer."*<sup>4</sup> This was based on the use of Androgen Deprivation Therapy (ADT) like Lupron as backbone therapy in pivotal trials of apalutamide (SPARTAN)<sup>5</sup> and enzalutamide (PROSPER)<sup>6</sup> for prostate cancer. ICER stated that there was no evidence that Lupron was the background ADT in the PROSPER trial and concluded that Lupron had unsupported new clinical evidence. However, through AbbVie's discussion with the FDA, Lupron is the only GnRH agonist to have received the new label language update and confirmed its important role in helping cancer patients.
- In limiting the assessment to indications representing greater than 10 percent use, ICER excluded HUMIRA's clinical and economic evidence in smaller patient populations, including rare conditions (i.e., hidradenitis suppurativa and uveitis) and pediatric populations (i.e., pediatric ulcerative colitis for which the FDA expanded HUMIRA use in 2020) that reflect our commitment to innovation and improvement in net health benefit to underserved populations with high unmet needs.<sup>7</sup>
- Citing Chambers, 2019<sup>8</sup> as a well-performed observational study conducted to address the safety of HUMIRA in pregnancy and yet concluding it did not meet the criteria of moderate to high quality evidence raises into question the subjective nature of ICER's rating of new quality evidence and additional net health benefit. Dismissing a valid study without an objective basis raises significant questions as to ICER's approach.

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 Part D and Medicaid ultimately pay for drugs. Unlike list prices, data on net prices are not readily available. SSR Health is a database that estimates net drug prices of drugs manufactured by publicly traded companies by dividing overall manufacturer revenues for a given drug (as reported to the US Securities and Exchange Commission and in other industry reports) by the total number of units dispensed (according to data from Symphony Health).<sup>9</sup> **SSR Health calculations of net drug prices are estimates and limited by uncertainty and quality along the drug supply chain.**

**As outlined above, in addition to clinical evidence, AbbVie believes that the totality of evidence must be evaluated as part of any value measurement.** AbbVie continually invests in the development of new patient-centric enhancements (e.g., citrate-free HUMIRA, thinner needle, new dosing configurations, etc.) and patient support programs (e.g., AbbVie Complete, AbbVie's Patient Assistance Program). Pursuing development of these programs are part of AbbVie's ongoing commitment to advance and improve the patient experience. 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 considered or 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 that provide access to patients for the vital innovative therapies that they need and deserve.

## References

<sup>1</sup> <https://www.phrma.org/cost-and-value/principles-for-value-assessment-frameworks>

<sup>2</sup> [https://icer.org/wp-content/uploads/2021/04/UPI\\_2021\\_Working\\_Protocol.pdf](https://icer.org/wp-content/uploads/2021/04/UPI_2021_Working_Protocol.pdf)

<sup>3</sup> Neumann, PJ, et al. ISPOR Task Force Report. Value in Health 21 (2018): 119-123

<sup>4</sup> [https://www.rxabbvie.com/pdf/lupronuro\\_pi.pdf](https://www.rxabbvie.com/pdf/lupronuro_pi.pdf)

<sup>5</sup> Smith MR, et al. The New England Journal of Medicine. 2018.

<sup>6</sup> Sternberg CN, et al; PROSPER Investigators. N Engl J Med. 2020 Jun 4;382(23):2197-2206.

<sup>7</sup> <https://www.rxabbvie.com/pdf/humira.pdf>

<sup>8</sup> Chambers CD, et al. PLoS ONE 14(10): e0223603. <https://doi.org/10.1371/0223603>

<sup>9</sup> Feldman WB, et al. JAMA Health Forum. 2021;2(6):e210626.doi

Bausch Health has committed to continued research across our portfolio with the goal of providing the clinical and health economic data that allows for informed decision-making. This, in tandem with our commitment to maximize affordable access to our therapies, has driven our approach to XIFAXAN<sup>®</sup> (rifaximin 550 mg tablets), a critical medication for managing gastrointestinal disease.

Consequently, we are compelled to highlight our concerns regarding the ICER Unsupported Price Increase (UPI) assessment of XIFAXAN<sup>®</sup> for the years 2020 and 2021, particularly the lack of transparency around the process itself, as well as the rejection of relevant, peer-reviewed health economic research that has helped ensure that our pricing actions are aligned with the product's value.

First, we wish to highlight that ICER initially miscalculated our net sales revenue. We requested that ICER correct this error, and after providing ICER with additional, non-public details, ICER cut its estimate by nearly half of net revenue increase due to price increases. Bausch Health never received an explanation process that led to the original error, eroding our ability to supply the necessary data to ensure accuracy.

We also question the usefulness of including XIFAXAN<sup>®</sup> in the report at all. ICER estimates that the net price increase on XIFAXAN<sup>®</sup> was 3.0%, a figure that is substantially below ICER's estimate of medical inflation. When adjusted for inflation, the price of XIFAXAN<sup>®</sup> fell, making the inclusion of the medicine an unusual choice in a report nominally about price increases.

Secondly, ICER inappropriately excluded research from its review. Last year, in the 2020 UPI assessment, Bausch Health provided two pieces of cost-effectiveness evidence (*Bozkaya D, 2014; Jesudian AB, 2020*) to support the value of XIFAXAN<sup>®</sup>. At that time, ICER excluded both publications with the same rationale: "*Study published outside of the timeframe of our review,*" implying that the *Bozkaya* paper was too old to have had an impact on our pricing decisions and that the work by *Jesudian AB* was too recent.

So, we were surprised when – after re-submitting the *Jesudian AB* publication for this year's review – ICER again refused to consider it, despite the study's relevance and publication during the ICER "Evidence Review Period" of January 2019 – December 2020.

In the 2021 UPI preliminary assessment of XIFAXAN<sup>®</sup> (dated September 13, 2021), *Jesudian AB* was excluded with the following reason provided by ICER: "*Previously known information about rifaximin related to cost.*" We dispute this characterization and hold that ICER's exclusion of *Jesudian AB* is unjustified.

*Jesudian AB* featured a cost-effectiveness analysis (CEA) model amongst patients with overt hepatic encephalopathy (HE), comparing rifaximin 550 mg twice daily with lactulose monotherapy from a U.S. third-party perspective over a lifetime horizon. The *Jesudian AB* study used updated and proximate model inputs such as life expectancy after liver transplantation from UNOS 2016 report. This UNOS 2016 update includes meaningful changes in estimates of the



life expectancy after liver transplantation and has a major impact on cost-effectiveness results and therefore the value delivered by XIFAXAN<sup>®</sup>.

*Jesudian AB* also uses updated health state utilities, derived from *Guest JF, 2014* which uses the time trade-off and standard gamble method to estimate utilities specific to the HE population, and the research used more current cost data. The *Jesudian AB* study shows that the incremental cost-effectiveness ratio per quality adjusted life years gained (in 2018 dollars) for rifaximin + lactulose vs. lactulose monotherapy is \$29,161, nearly 10% higher than previous estimates and still well within common accepted willingness-to-pay thresholds.

The publication year (2020) of *Jesudian AB* not only falls in the ICER 2021 Review Period but is also a key building block of the CEA model (i.e., model inputs and CEA estimates [2018 \$]), reflecting the most recent data available to the authors for their CEA analysis and publication. This study provides evidence that supports and augments the value of XIFAXAN<sup>®</sup>.





**October 12, 2021**

**RE: ICER's Unsupported Price Increase Assessment for natalizumab (TYSABRI®)**

Biogen appreciates the opportunity to comment on ICER's draft Unsupported Price Increase Assessment for TYSABRI. In this assessment, ICER aims to review new evidence for TYSABRI over a 24-month period (January 1, 2019 – December 31, 2020) on efficacy, safety, and economic outcomes, as well as other potential supporting rationale to evaluate the increase in price from 2019 to 2020.

**Biogen Disagrees with ICER's Exclusion of 23 References for TYSABRI That Were Published in 2019 – 2020 and Provided by Biogen**

Biogen provided 23 references relating to TYSABRI that were published in 2019 and 2020. ICER excluded all of these references in its assessment. Additionally, ICER did not conduct a search for additional new evidence. In addition to independent publications, Biogen has sponsored research that resulted in the publication of over 15 articles and over 70 presentations at various Neurology congresses in 2019-2020.

Biogen believes that all of the references published in 2019 - 2020 consistently demonstrate TYSABRI's long-term efficacy and safety, its comparative effectiveness, and its significant impact on quality of life and other patient-reported outcomes (PROs) for patients with MS.<sup>1-23</sup> Biogen respectfully disagrees with the exclusion of these studies from ICER's assessment as they provide important new and confirmatory clinical information on TYSABRI.

While observational studies do not always merit a similar quality grade to that of randomized clinical trials (RCTs), it is disappointing that all of the observational studies for TYSABRI that Biogen submitted for this assessment have been excluded in this report as they provide valuable and important data and evidence to inform clinical care for people living with MS. It is mentioned in the GRADE guidelines that rigorous observational trials can provide stronger evidence than uncontrolled case series and that if the observational studies have special strengths, they should be considered high quality evidence in the evaluation. The study designs and limitations within the STRIVE<sup>2,4,12</sup>, TYGRIS<sup>13</sup> and TOP<sup>1,3</sup> observational studies provided as publication support are representative of real-world populations on TYSABRI treatment and in which the endpoints are unique to the study populations. STRIVE provides information regarding long-term use of TYSABRI in a JCV-antibody negative population; TYGRIS was designed to capture long-term safety data in clinical practice; and TOP, one of the longest ongoing analyses of MS patients on TYSABRI therapy, has recently been extended to include up to 15 years of experience. Excluding these studies<sup>1-23</sup> dismisses a large volume of previously unpublished, peer-reviewed, scientific evidence, often for different patient subgroups than what was observed in the clinical trials, as well as longer follow-up durations and different data sources, and / or countries. Furthermore, these studies consistently show that TYSABRI efficacy and safety is similar to what has been seen in the pivotal trials even for periods of over 10 years.

Biogen also disagrees with the designation of “previously known information” for the TYSABRI references<sup>2, 3, 8, 12-16, 19, 22</sup> provided in the initial review. These studies add significant additional value for patients and HCPs, and while the results are generally consistent with what has been published before, both the study populations (real-world or special populations) and the efficacy and safety data over a longer duration of treatment (i.e., over 10 years) were not previously known.

Biogen strongly recommends that ICER re-evaluate the observational studies supporting the benefits of TYSABRI and consider approaches for assessing the value of real-world, observational research, which is an important element to inform clinical decision-making and patient care. Reports such as these have the potential to devalue or reduce incentives for manufacturers to generate more evidence on the value of disease-modifying therapies, even ones that have been on the market for 15 years, to continually inform on, and support, the safety, efficacy, and patient benefits of treatments for life-long diseases. This, in turn, limits the evidence available to HCPs and the MS community to inform and improve treatment decision-making.

**Biogen Has Continued Its Commitment to Invest in Studies, including Randomized Clinical Trials (RCTs), Registries, and Real-World Evidence Generation, to Further Demonstrate TYSABRI’s Value Proposition, Including Long-Term Efficacy and Safety, Comparative Effectiveness, Patient Reported Outcomes and Addressing Data Gaps Across Multiple Patient Types**

Since the TYSABRI launch 15 years ago, Biogen has invested significantly in studies that further inform on, and demonstrate, TYSABRI’s value proposition to better assist payers and clinicians with their decision-making regarding treatment of relapsing MS.

One large area of continual investment for TYSABRI is PML and understanding the risk of PML with TYSABRI treatment. This has been a significant research interest for Biogen that has led to a number of important advances in our understanding of PML and TYSABRI treatment related risk of PML. For example, the NOVA Study (NCT03689972) is a randomized, controlled, open-label, rater-blinded, Phase 3b study to evaluate the efficacy, safety, and tolerability of 6-weekly natalizumab dosing intervals (Q6W) in patients with RRMS who switch to an extended Q6W dosing after one year of 4-weekly standard interval (Q4W) treatment with natalizumab, in relation to continued Q4W treatment. Previous retrospective studies utilizing the US TOUCH™ Prescribing Program database have led to the understanding that extending the dosing schedule from Q4W to Q6W for patients treated with TYSABRI leads to a significant reduction in the risk of PML.<sup>20</sup> The data from the NOVA study brings value to HCPs and provides important information to support individualized treatment decision-making by assessing whether efficacy is maintained when reducing the exposure-dependent risk of PML. The study was initiated in December 2018 and primary results were publicly announced in August of 2021.

Multiple prospective, observational studies are currently ongoing, including, but not limited to, TOP<sup>1,3</sup>, which is one of the longest ongoing real-world safety and efficacy trials for TYSABRI.

This trial has recently been extended to 15 years to provide further long-term data and demonstrates Biogen's commitment to continual generation of long-term data across multiple MS patient types in real-world clinical practice. Biogen also sponsors various studies, including MS Partners Advancing Technology and Health Solutions (MS PATHS) to foster collaboration between leading MS centers in U.S. and Europe to help transform patient care by generating standardized data collection protocols from a diverse, real-world clinical practice patient population. An example of this continued commitment to improving patients' quality of life was provided as a presentation<sup>19</sup> and later developed into a peer-reviewed accepted publication in 2021. The analysis uses the standardized data from MS PATHS based on a real-world patients' cohort and shows a strong positive impact of TYSABRI on various quality-of-life (QoL) measurements. Patient reported outcomes (PROs) have become an important measurement that adds to the clinical profiles of available treatments beyond randomized clinical trials and have been proven to be critical for patient adherence to DMTs for a life-long disease. We believe this ongoing investment provides important and valuable information to the MS community.

**Biogen Has Also Continued Its Commitment to Invest in TYSABRI-associated safety risk mitigation programs and industry-leading services to ensure that patients experience the full benefits of taking TYSABRI**

Biogen recognizes that managing a complex disease such as MS encompasses additional components beyond developing and offering therapies such as TYSABRI, and that MS patients and healthcare providers also value safety risk mitigation measures when making a DMT treatment decision. Therefore, Biogen has consistently been a leader in providing services to MS patients and their healthcare providers. We continue to improve our solutions that expand upon the value delivered from our medicines such as TYSABRI. TYSABRI-associated safety risk mitigation programs offered by Biogen include:

- **The TOUCH<sup>®</sup> Prescribing Program:** Only prescribers, infusion centers, and their associated pharmacies enrolled with the program are able to prescribe, distribute, or infuse the product. TYSABRI must be administered only to patients who are enrolled in and meet all the conditions of the TOUCH Prescribing Program
- **Anti-JCV antibody testing for PML risk stratification:** Anti-JCV antibody testing via the STRATIFY JCV<sup>™</sup> Dx Select antibody ELISA is a validated tool developed by Biogen to assess the risk of developing TYSABRI-associated PML in MS and enables an individualized patient management approach

Patient support services offered by Biogen include: One-on-one phone support from support coordinators, free 24/7 access by phone to nurse educators, information about TYSABRI treatment and support services, benefits investigations to clarify patient coverage options, and insurance counseling, including help navigating changes due to the health care reform law.

As a leader in MS, Biogen understands the importance of research to generate long-term follow-up data on the safety, efficacy/effectiveness and patient reported outcomes of TYSABRI as well as the importance of providing TYSABRI-associated safety risk mitigation programs, and industry-leading services to ensure that patients experience the full benefits of taking TYSABRI.

We respectfully disagree with the assessment on TYSABRI and believe that this evaluation does not represent the value proposition of TYSABRI.

### References

1. Butzkueven H, Kappos L, Wiendl H, et al. Long-term safety and effectiveness of natalizumab treatment in clinical practice: 10 years of real-world data from the Tysabri Observational Program (TOP). *J Neurol Neurosurg Psychiatry*. 2020;91:660-668.
2. Perumal J, Fox RJ, Balabanov R, et al. Natalizumab is associated with no evidence of disease activity and with improvement in disability and cognitive performance in anti-JC virus seronegative patients with early relapsing-remitting multiple sclerosis: STRIVE 4-year results. *Mult Scler*. 2019;25(S2):741-742.
3. Wiendl H, Spelman T, Butzkueven H, et al. Real-world disability improvement in patients with relapsing-remitting multiple sclerosis treated with natalizumab in the Tysabri Observational Program. *Mult Scler*. 2020 Jun 24 [Epub ahead of print]
4. Perumal J, Balabanov R, Balcer L, et al. Disability improvement in early multiple sclerosis patients treated with natalizumab in STRIVE, a phase 4, multicenter observational study. Presented at the Americas Committee for Treatment and Research in Multiple Sclerosis 2020 Forum; February 27–29, 2020; West Palm Beach, FL
5. Landi D, Portaccio E, Bovis F, et al. Continuation of natalizumab versus interruption is associated with lower risk of relapses during pregnancy and postpartum in women with MS. Abstract (338), ECTRIMS, 2019, Stockholm, Sweden
6. Demortiere S, Rico A, Maarouf A, et al. Maintenance of natalizumab during the first trimester of pregnancy in active multiple sclerosis. *Mult Scler*. 2020 Mar 23 [Epub ahead of print]
7. Yeh M, et al. Pregnancy in a modern day multiple sclerosis cohort: Predictors of relapse during pregnancy. Poster (PS12.04), ECTRIMS, 2019, 2020, Washington D.C., US
8. Portaccio E, Tudisco L, Pastò L, Razzolini L, Prestipino E, Fonderico M, et al. Pregnancy in women with multiple sclerosis treated with Natalizumab: a re-appraisal of maternal risks in a long-term follow-up. Poster (P409), ECTRIMS, 2019, Stockholm, Sweden
9. Peng A, Qiu X, Zhang L, et al. Natalizumab exposure during pregnancy in multiple sclerosis: a systematic review 2019. 396: 202-205
10. Ghezzi A, Comi G, Grimaldi LM, et al. Pharmacokinetics and pharmacodynamics of natalizumab in pediatric patients with RRMS. *Neurol Neuroimmunol Neuroinflamm*. 2019;6:e591
11. Margoni M, Rinaldi F, Riccardi A, Franciotta S, Perini P, Gallo P. No evidence of disease activity including cognition (NEDA-3 plus) in naive pediatric multiple sclerosis patients treated with natalizumab. *J Neurol*. 2020 Jan;267(1):100-5
12. Perumal J, Balcer L, Balabanov R, et al. Anti-JC virus seronegative African American patients with early multiple sclerosis treated with natalizumab in STRIVE: a post-hoc analysis. Presented at the Americas Committee for Treatment and Research in Multiple Sclerosis 2020 Forum; February 27–29, 2020; West Palm Beach, FL

13. Foley J, Carrillo-Infante C, Smith J, Evans K, Ho PR, Lee L, et al. The 5-year Tysabri global observational program in safety (TYGRIS) study confirms the long-term safety profile of natalizumab treatment in multiple sclerosis. *Mult Scler Relat Disord*. 2019 Nov 21;39:101863
14. Cohen M, Mondot L, Bucciarelli F, et al. BEST-MS: A prospective head-to-head comparative study of natalizumab and fingolimod in active relapsing MS. *Mult Scler* 2020 Oct 30; 1352458520969145 doi: 10.1177/1352458520969145.
15. Julian GS, Rosim RP, Carneseca EC, Rigolon J. Annualized hospitalization rate with natalizumab vs fingolimod in second-line treatment for RRMS in the public healthcare system in Brazil: a claim database approach. *PLoS One*. 2020;15:e0229768
16. Butzkueven H, Licata S, Jeffery D, et al. Natalizumab versus fingolimod for patients with active relapsing-remitting multiple sclerosis: results from REVEAL, a prospective, randomised head-to-head study. *BMJ Open*. 2020;10:e038861
17. Efthimiou O, Acosta C, Saunders-Hastings P, Pellegrini F. Meta-analysis of randomized controlled trials and real-world evidence comparing natalizumab and fingolimod for relapsing-remitting multiple sclerosis. Presented at MSVirtual2020: 8th Joint ACTRIMS-ECTRIMS Meeting; September 11–13, 2020. P0108
18. Spelman T, Acosta C, Hyde R, et al. Comparative effectiveness of natalizumab, fingolimod, and first-line therapies for rapidly evolving severe relapsing-remitting multiple sclerosis. Presented at MSVirtual2020: 8th Joint ACTRIMS-ECTRIMS Meeting; September 11–13, 2020. P0859
19. Hersh C, Kieseier B, de Moor C, Miller D, Campagnolo D, Williams J, et al. Impact of natalizumab on quality of life in a real-world cohort of patients with multiple sclerosis: results from MS PATHS p1036 (poster). Presented at the 8th Joint ECTRIMS meeting 2020; 2020
20. Zhovtis-Ryerson L, Foley J, Chang I, et al. Natalizumab extended interval dosing (EID) is associated with a reduced risk of progressive multifocal leukoencephalopathy (PML) than every-4-week (Q4W) dosing: updated analysis of the TOUCH<sup>®</sup> Prescribing Program database. *Neurology*. 2020;94(15 suppl):1988
21. Kagstrom S, Falt A, Forsberg L, Berglund A, Hillert J, Nilsson P, et al. Improved clinical outcomes in patients treated with Natalizumab for at least 8 years – real-world data from a Swedish national post-marketing surveillance study (IMSE 1). Poster (P1383), ECTRIMS, 2019, Stockholm, Sweden
22. Capra R, Morra VB, Mirabella M, et al. Natalizumab is associated with early improvement of working ability in relapsing-remitting multiple sclerosis patients: WANT observational study results. *Neurol Sci*. 2020 Nov 17 [Epub ahead of print]
23. Chen J, Diouf I, Taylor B, Kalincik T, Van Der Mei I. Effects of natalizumab on patient-reported MS outcomes using prospective data from the Australian MS longitudinal study. Presented at MSVirtual2020: 8th Joint ACTRIMS-ECTRIMS Meeting; September 11–13, 2020. FC04.02



October 12<sup>th</sup>, 2021

**RE: ICER UPI Preliminary Assessment of KRYSTEXXA**

Horizon appreciates the opportunity to comment on ICER's Unsupported Price Increase ("UPI") preliminary assessment for KRYSTEXXA (pegloticase). Horizon disagrees with ICER's decision to exclude the 17 publications submitted by Horizon, which demonstrate meaningful new benefits for treatment with KRYSTEXXA. Horizon is committed to developing therapies that can improve the lives of people living with rare diseases, and our recent development efforts for KRYSTEXXA epitomize this commitment.

I. Horizon's Commitment to Patients with Rare Diseases

When we started Horizon in 2008, we 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.

Science and compassion must work together to transform lives. Our mission to develop medicines for rare, autoimmune and severe inflammatory diseases and to provide compassionate support comes from our strong and simple philosophy to make a meaningful difference for patients, providers and communities in need.

With over 7,000 known rare diseases affecting over 30 million Americans, we think differently about research and development in order to deliver therapies in new ways for the patients and communities we serve. We apply extensive research experience to target, design and execute research and development (R&D) programs that will have a profound impact on underserved patients who do not have many, if any, options.

At Horizon, patients come first, always. We provide a breadth of resources and support programs that help patients who are prescribed Horizon medicines throughout the duration of their journey. These programs ensure patients have access to our treatments regardless of their financial situation.

As a company, we are committed to addressing the long-term 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, including by supporting external studies to examine the impact of uric acid on different areas of the body through advanced imaging. Our efforts aim to identify early therapeutic options with the potential to produce immediate and marked benefit for patient communities.

Our efforts to expand the efficacy and safety profile of KRYSTEXXA through scientific data generation exemplify our ongoing commitment to patients.



## II. ICER's Determination Does Not Reflect the Clinical Value of New Evidence

### Supporting KRYSTEXXA

In 2010, KRYSTEXXA became and remains the first and only FDA-approved biologic for uncontrolled gout, a rare disease that can have crippling effects and significant disease burden on patients.<sup>1</sup> In the years since approval, Horizon has invested significantly in understanding and improving the safety and efficacy profile for KRYSTEXXA, including addressing debilitating tophi as shown by Figure 1. This includes the development of meaningful new clinical evidence during the Evidence Review Period (2019-2020) and beyond.



*Figure 1: Photographs of the patient's knees and hands before (left) and after (right) treatment with KRYSTEXXA, demonstrating significant visible reduction of tophi<sup>5</sup>*

Horizon submitted 17 studies published from 2019 to 2020 that demonstrate the clinical and economic value of KRYSTEXXA. ICER excluded these publications based on a range of justifications, including “intervention/comparison not relevant to scope,” “outcomes not relevant to scope,” “previously known information,” “indication accounts for less than 10% of use,” “study published outside of the timeframe of our review,” and “low quality evidence.” ICER’s exclusion of key scientific evidence that has already transformed the standard of care for uncontrolled gout compromises ICER’s ability to comprehensively and accurately assess the value of a product like KRYSTEXXA to patients, physicians, and payers.

Horizon submitted 12 publications related to a series of studies on the use of

<sup>1</sup> KRYSTEXXA (pegloticase injection) for intravenous infusion [prescribing information] Horizon; Schlesinger N and Lipsky PE. Pegloticase treatment of chronic refractory gout: Update on efficacy and safety. *Seminars in Arthritis and Rheum.* 2020;50(3):S31-S38.

immunomodulation (immune-modifying therapy) with KRYSTEXXA. Consistent with ICER's UPI Protocol, these studies benefitted the treatment landscape for uncontrolled gout, generating new evidence beyond "what was previously generally believed about a therapy (whether its clinical or economic effects)."<sup>2</sup> While KRYSTEXXA demonstrated rapid reduction in serum uric acid (sUA) level for people with uncontrolled gout in the clinical trials that were used as part of FDA approval, as with many biologic therapies, some people developed anti-drug antibodies (ADAs). Horizon engaged the clinical community to evaluate ways to improve effectiveness in these patients and invested significantly in clinical development programs to improve the response rate of 42% from the initial clinical trial.

Specifically, Horizon initiated a series of studies on the use of various immunomodulatory agents with KRYSTEXXA to help prevent or minimize ADA development. The majority of these results were published during the 2019-2020 Evidence Review Period, including studies related to co-administration of KRYSTEXXA with new immunomodulatory agents that previously had not been studied by Horizon prior to this time period. Two significant studies, for example, demonstrated substantial improvement in response rates and safety results:

- RECIPE: RECIPE is the first randomized, double-blind, multicenter trial to demonstrate an improvement in the efficacy of KRYSTEXXA administered concomitantly with mycophenolate mofetil with a lower incidence of infusion reactions. This study demonstrated significant improvement in the primary endpoint (percent of patients achieving a sUA of less than 6 mg/dL) comparing KRYSTEXXA/mycophenolate mofetil to KRYSTEXXA alone at Week 12 (86% compared to 40%,  $p=0.01$ ) as well as a reduced infusion reaction rate.<sup>3</sup> Nevertheless, ICER rejected this evidence, providing the following justification without further explanation: "intervention/comparison not relevant to scope." However, the intervention of a co-administrated immunomodulatory agent with KRYSTEXXA is highly relevant to the scope of a report investigating whether there is new evidence that provides a net benefit. This new data demonstrates a significantly improved response rate of 86% and supports physician decision-making in optimizing treatment with KRYSTEXXA.
- MIRROR-Open Label (OL): MIRROR-OL is a prospective, multicenter, open-label efficacy and safety study of KRYSTEXXA administered concomitantly with methotrexate. Although this clinical study demonstrated similarly improved

---

<sup>2</sup> 2021 UPI Protocol at 6.

<sup>3</sup> Khanna P, Khanna D, Cutter G 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. Oral presentation at the American College of Rheumatology Convergence; November 5 – 9, 2020; Virtual meeting.



efficacy and safety results as reported in RECIPE,<sup>4</sup> ICER rejected its inclusion, providing the following justification: “study published outside of the timeframe of our review.” However, the study was e-published on September 15, 2020, within the 2019-2020 Evidence Review Period. Additionally, like RECIPE, the MIRROR-OL study provided new data to support patient and physician decision-making to optimize uncontrolled gout management. This study also led to additional clinical development efforts with the initiation of MIRROR RCT in 2019, a Phase 4 multicenter, randomized controlled study of KRYSTEXXA administered concomitantly with methotrexate. MIRROR RCT will build on the compelling evidence developed during the Evidence Review Period regarding concomitant use of immunomodulatory agents, and Horizon plans to submit the MIRROR RCT study to the FDA to support an updated label for KRYSTEXXA.

The release of these and other new immunomodulation studies has already improved adoption of concomitant administration of KRYSTEXXA, demonstrating the benefit of these studies to the treatment landscape. Since 2018, there has been a paradigm shift in care with a five-fold increase in the adoption of immunomodulation use with KRYSTEXXA in the treatment of uncontrolled gout.

ICER’s decision to exclude all 12 of Horizon’s peer-reviewed immunomodulation publications from consideration in the UPI Report – generally on the basis that they involve an “intervention/comparison not relevant to scope” or “outcomes not relevant to scope” – is inconsistent with the value and significance of these studies. As a threshold matter, ICER has not adequately defined these terms, failing to provide sufficient criteria or description of studies that ICER would consider relevant to scope. The lack of such basic transparency undermines the credibility of ICER’s justifications for such exclusions. Substantively, it is difficult to understand how studies demonstrating improved efficacy and safety of KRYSTEXXA via concomitant use of immunomodulatory agents could possibly 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 physician community.

Additionally, the profound impact of this research and progress on people who have been suffering the physical and emotional burden of uncontrolled gout for decades should not be discounted. Uncontrolled gout patients have often endured a long clinical journey suffering from diagnostic delays and under-treatment. These patients often continue to suffer from constant and painful acute gout attacks due to this mismanagement and misunderstanding. Excluding these important data on immunomodulation continues to add to the neglect of this patient population.

---

<sup>4</sup> Botson J, Tesser JRP, Bennett R et al. Pegloticase in combination with methotrexate in patients with uncontrolled gout: a multicenter, open-label study (MIRROR). *The Journal of Rheumatology*. 2021;48(5):767-774. Epub 2020 Sep 15.

Horizon also submitted five publications reflecting development efforts to help clinicians understand the benefits of KRYSTEXXA among patients with comorbidities.

Uncontrolled gout patients are known to have specific comorbidities including hypertension, dyslipidemia, chronic kidney disease, diabetes, coronary artery disease and cardiac failure, which add complexity to their management and increase their morbidity, mortality, and health care utilization. Horizon's development efforts with respect to these comorbidities contributes meaningful progress toward understanding KRYSTEXXA treatment across diverse and complex patient populations, and similarly should be considered meaningful new evidence supporting the value of KRYSTEXXA.

The 17 publications submitted in support of KRYSTEXXA are even more critical given that uncontrolled gout is a rare disease. Drug development for rare diseases is challenging for many reasons, including complex biology, lack of understanding regarding the natural history of rare diseases, and the inherently small patient population with resulting difficulties in patient recruitment.<sup>5</sup> For example, clinical trial enrollment for RECIPE involved recruiting 42 eligible patients over a period of 18 months from five rheumatology practices; 32 of these patients were ultimately included in the study, which demonstrated significant improvement in response rate. This study demonstrates the recruitment challenges for clinical trials in rare diseases. Additionally, data generation through robust clinical trials takes years, whereas the ICER UPI report captures only a two-year snapshot of an overall clinical development program. Horizon believes its investment in clinical development supports the value and pricing of KRYSTEXXA, and we encourage ICER to ensure its UPI report criteria are applied in a manner that recognizes clinical development may be ongoing outside of the review period chosen.

### III. Conclusion

In conclusion, Horizon has invested substantially in research and development efforts to improve the safety and efficacy of KRYSTEXXA in the various patient populations who are afflicted with uncontrolled gout. We disagree with ICER's evaluation of the 17 publications submitted, specifically, the exclusion of MIRROR-OL and RECIPE, which demonstrate the new clinical benefit of KRYSTEXXA plus immunomodulatory agents.

Dr. Jeffrey Sherman  
Executive Vice President, Chief Medical Officer  
[jsherman@horizontherapeutics.com](mailto:jsherman@horizontherapeutics.com)

---

<sup>5</sup> Rare Disease at FDA. Food and Drug Administration Website.  
<https://www.fda.gov/patients/rare-diseases-fda>. Accessed Aug. 31, 2021.

## **Novartis Response to ICER's 2021 Unsupported Price Increase Protocol for Promacta (eltrombopag)**

12-October-2021

Novartis Pharmaceuticals Corporation is committed to investing in research that will improve the lives of those who suffer from diseases with a high burden and unmet need, such as adult and pediatric patients with immune thrombocytopenia (ITP) and severe aplastic anemia (SAA). This document responds to the 2021 Unsupported Price Increase (UPI) assessment [1] from Institute for Clinical and Economic Review (ICER), which focuses on only new evidence published in the past 2 years.

ICER's approach to its UPI assessment of Promacta® (eltrombopag) is flawed, in a number of ways: (1) it only evaluates price changes and does not perform a systematic evaluation of treatment value, (2) it does not fully encapsulate totality of new evidence supporting the value of eltrombopag as it is limited to recent clinical studies and excludes evidence on broader societal impacts, and (3) ICER's price calculations using SSR Health data underestimate the rebate rate and also these data miss a proportion of units distributed through specialty pharmacies, resulting in an overestimate of ICER's net price change calculation for eltrombopag. In short, ICER's UPI assessment not only does not appropriately value eltrombopag, but its net price calculations used are also inaccurate.

**Further, Novartis would like to highlight six (6) areas where new evidence reinforces the value of eltrombopag:**

1. Update of Promacta (eltrombopag) US Prescribing Information to include "persistent" ITP, per clinical treatment guidelines
2. Data on eltrombopag real-world effectiveness
3. Analysis of eltrombopag superior platelet response
4. Research on eltrombopag long-term safety
5. Real-world evidence on the patient preference for oral administration, a potential benefit during COVID-19 pandemic
6. Analysis of decreases in annual payer cost due to less intensive dosing for eltrombopag

**In addition to strong clinical evidence, new health economic data demonstrate that eltrombopag is a cost-effective medicine with positive budget impact for payers:**

7. Eltrombopag US private payor budget impact model
8. Eltrombopag cost-effectiveness analysis versus common treatment alternatives

Additional details on these 8 points are discussed below.

**Further, Novartis has continued to invest in areas where patients can benefit.** Children PINES (NCT03939637), for example, is a phase III trial of eltrombopag against standard first-line management for newly diagnosed ITP pediatric patients [2]. The TAPER trial (NCT03524612) is a phase II, open-label, trial examining whether individuals with ITP are able to achieve sustained remission after tapering off drug [3]. The Children PINES and TAPER trials are just two examples of Novartis' commitment to investing in high-quality clinical evidence to improve patients' outcomes.

## **1. Update of Promacta (eltrombopag) US Prescribing Information to include “persistent” ITP, per clinical treatment guidelines**

Per the 2019 guideline from the American Society of Hematology, persistent ITP is defined as ITP duration of 3-12 months. Novartis received approval to modify the ITP indication statement to add “persistent” to remain consistent with the patient population enrolled in the registration clinical studies with adult and pediatric ITP, allowing patients to start on eltrombopag 3 months after ITP diagnosis and 1L treatment failure [4, 5].

In the past, ITP was categorized based on the length of time from initial diagnosis into 'acute' ITP that lasted for up to 6 months from initial diagnosis and 'chronic' ITP that lasted beyond 6 months from initial diagnosis. The International Working Group (IWG) released updated guidelines in 2009 (Rodeghiero et al. 2009) [4], in which ITP was divided into 'newly diagnosed' ITP (lasting up to 3 months from diagnosis), 'persistent' ITP (lasting between 3 and 12 months from diagnosis) and 'chronic' ITP (lasting more than 12 months from diagnosis). This classification was recently reaffirmed by the American Society of Hematology (ASH), which suggests use of thrombopoietin receptor agonists (TPO-RA) as a treatment option in persistent ITP (lasting  $\geq 3$  months) patients who are corticosteroid-dependent or unresponsive to corticosteroids to achieve durable responses (Neunert et al. 2019) [5].

Study 773B randomized 114 patients (2:1) to eltrombopag 50 mg or placebo. Of 60 patients with documented time since diagnosis, approximately 17% met the definition of persistent ITP. Study 773A randomized 117 patients (1:1:1:1) among placebo or 1 of 3 dose regimens of eltrombopag, 30 mg, 50 mg, or 75 mg each administered daily. Of 51 patients with documented time since diagnosis, approximately 14% met the definition of persistent ITP [5].

## **2. Data on eltrombopag real-world effectiveness**

New observational comparative, prospective, retrospective, and case studies have shown that eltrombopag improves platelet counts, lowers the risk of bleeding related events, thromboembolic events, and lowers risk of long-term complications (e.g., pneumonia, septicemia). Specifically, new evidence proves that eltrombopag is effective and efficacious across a range of patient populations including: (i) second-line (2L) adult patients with chronic immune thrombocytopenia (cITP); (ii) elderly patients with primary or secondary ITP, (iii) and for patient populations outside the US.

Recent studies show that **eltrombopag can improve platelet counts, lower risks of bleeding related events, and lower risk of long-term complications for 2L treatment of cITP in adults.**

- Vianello, F. et al. 2019 show the use of eltrombopag and other TPO-RA's for ITP patients in persistent phase as 2L therapy can be responsive [6].
- Lal et al. 2020 conducted a retrospective observational cohort study of patients  $\geq 18$  years who initiated 2L treatment with eltrombopag for cITP. Patients who received eltrombopag had statistically significantly higher chance of reaching a treatment-free period following therapy (33%) and fewer bleeding related episodes (25.5%) and thromboembolic events (11.6%) [7].
- In Ruiz-Negron et al. 2019's retrospective observational study of US Veterans receiving 2L treatment for cITP, there were statistically significantly fewer long-term complications with

TPO-RAs versus rituximab (hazard ratio (HR)=0.73; 0.62-0.85), including a lower risk of pneumonia (HR =0.66; 0.50-0.85) [8].

One study also demonstrates that **eltrombopag has proven efficacy and effectiveness in elderly patients for the treatment of primary and secondary ITP.**

- In this retrospective, multicenter study conducted by Gonzalez-Lopez et al. 2020 elderly patients with primary or secondary ITP, 82% had a response and 75% had a complete response based on platelet levels. Further 72% of patients had a response at 3 months (58% achieved CR). Median time to platelet response was 14 days and median duration of response was 334 days [9].

**Global studies also demonstrated eltrombopag's short- and long-term effectiveness.**

- In France, Moulis G. et al. 2021 conducted a retrospective real-world evidence analysis that demonstrated eltrombopag's safety and effectiveness in adults treated with eltrombopag within 6 months of ITP diagnosis. Using the French CARMEN registry, 48 had a platelet count <30 G/L at eltrombopag initiation; among them, 39 (81.3%) achieved overall response (platelet count  $\geq$ 30 G/L) and 35 (72.9%) complete response (platelet count  $\geq$ 100 G/L) [10].
- In India, Mishra K. et al. 2020 using 2012-2019 retrospective, single-center data found that median time to response was 35 days and the cumulative overall response rates (ORR) at day 30, day 60 and day 90 were 41.5%, 69.8%, and 81.1% respectively. Eltrombopag among adult ITP patients in India was well-tolerated and yielded excellent overall response [11].
- In Spain, Mingot-Castellano, M.E. et al. 2018 led a retrospective study of 100 adult ITP patients and found that 25% of patients with newly diagnosed or persistent ITP and 7.2% with chronic responded and maintained their response when TPO-RAs were stopped [12].

### **3. Analysis of eltrombopag superior platelet response**

A systematic review and network meta-analysis (NMA) of treatment for adult persistent ITP found that romiplostim and eltrombopag had improved platelet response and platelet count compared to placebo [13]. Twelve randomized controlled trials of 2L treatments of adult with persistent ITP were eligible for the NMA. Eltrombopag and romiplostim had the best platelet response; eltrombopag had a non-significant advantage [risk ratio (RR)=1.10 (95% CI: 0.46, 2.67)] against romiplostim. Both treatments were superior to rituximab and recombinant human thrombopoietin+rituximab with eltrombopag corresponding RRs of 4.56 (1.89, 10.96) and 4.18 (1.21, 14.49).

### **4. Research on eltrombopag long-term safety**

In a meta-analysis that evaluated the efficacy and safety of eltrombopag in adults and children with ITP, researchers found safe and efficient use of eltrombopag in ITP versus placebo. The meta-analysis included 7 studies with a total of 765 patients (606 adults and 159 children). The number of patients needing rescue treatment and number of bleeding incidents were reduced in the group that received eltrombopag versus placebo. The total number of adverse effects did not statistically differ between the two groups [14]. Additionally, a prospective, multi-center Phase 2 trial of 51 patients found that eltrombopag remains a safe treatment option. Twenty-three patients (45%) reported a total of 51 AEs

and 16 SAEs, with only 5 AEs considered treatment related. Eltrombopag was interrupted because of toxicity in three patients (6%) [15]. Further, a retrospective real-world study using the French CARMEN also found that 16.8% of patients experienced adverse drug reactions [10].

### **5. Real-world evidence on the patient preference for oral administration, a potential benefit during COVID-19 pandemic**

The ITP World Impact Survey (I-WISH) [16], a cross-sectional survey of 1,507 patients that evaluated the impact of ITP on health-related quality of life, found that patients treated with anti-CD20 agents reported high overall satisfaction regarding control of their ITP for those receiving thrombopoietin receptor agonists (76%; n = 182/ 240). Additionally, 90% patients preferred orally administered ITP over an injection [17]. The oral formulation may provide value during the COVID-19 pandemic as it may reduce the risk of transmission from having to visit an office to receive treatment and increased patient access when physician offices were closed during the COVID-19 pandemic.

### **6. Analysis on decreases in annual payer cost due to less intensive dosing for eltrombopag**

Cohort studies have shown that 3%-33% of patients with ITP may go into remission and maintain hemostatic platelet counts after tapering and discontinuing TPO-RAs [18]. Based on this recent evidence, annual per patient payer cost is likely to fall as clinicians become aware that tapering and eventually discontinuing treatment is a feasible option for patients with stable response. A modified Delphi panel of US clinical experts concluded that TPO-RA can be tapered by decreasing the dose periodically to the minimum available dose but maintaining the time interval between doses [18]. The Delphi Panel findings are supported by other studies which found that intermittent eltrombopag dosage in primary ITP provides similar safety and efficacy as daily dosing [19]. A retrospective review in 508 adult patients treated with eltrombopag for primary ITP found that patients were able to maintain response after treatment discontinuation ( $\geq 6$  months) and long-term response after discontinuation ( $\geq 36$  months). Seventy-four patients (14.6%) successfully discontinued eltrombopag, and 38 patients (51.3%) maintained treatment-free response at 36 months [20]. A retrospective analysis that assessed ITP newly diagnosed, non-splenectomized patients with ITP who received TPO-RAs, found that the overall response rate was 79.2%, while the discontinuation rate in all ITP patients were 41.6% [21]. Another retrospective study found that the discontinuation rate for patients with a stable response was 40% in patients with newly diagnosed and persistent ITP patients [22]. In Italy, a study confirmed that responders were able to taper and discontinue use of TPO-RAs [15].

### **7. Eltrombopag US private payor budget impact model**

Results from a budget impact model (BIM) from the US private payer perspective show that the introduction of eltrombopag in 2L cITP is predicted to yield cost savings [23]. The model has a 3-year time horizon and assumed a hypothetical 1-million member US private health plan. Over 3 years, total costs in the scenario without eltrombopag were \$5.63 million, whereas total costs in the scenario with eltrombopag were \$4.46 million. The model estimated the total budget impact, from the addition of



eltrombopag to a health plan formulary for 2L cITP, to be an average of -\$1.18 million over the course of the 3-year time horizon. On a per patient basis, average savings were estimated to be -\$35,632 over the course of the 3-year time horizon.

A cost-minimization analysis found that eltrombopag resulted in \$64,770 lower cost compared to romiplostim from a US health plan perspective [24]. The base case used a commercial plan perspective, with average dosing of 51.5 mg/day for eltrombopag and 4.20 µg/kg/week for romiplostim; eltrombopag remained the less costly option for all plan types and assumptions. Based on a hypothetical commercial plan with 1 million members and an estimated 15 cITP patients receiving romiplostim, potential annual savings for switching all patients from romiplostim to eltrombopag was \$971,554 or \$0.08 per member per month.

In addition to BIM, real-world data support the economic value of eltrombopag. A retrospective claims database study (2014-2017) (n=82) evaluating healthcare resource use and direct costs before and after eltrombopag use among patients with severe aplastic anemia showed significantly lower hospitalization, ER and outpatient visits following 6-month use of eltrombopag; with an overall mean reduction in total all-cause costs of \$29,391 (SD= \$137,770) due to substantial reduction in hospitalization costs and outpatient costs [25].

## **8. Eltrombopag cost-effectiveness analysis versus common treatment alternatives**

A recent cost effectiveness analysis compared eltrombopag with romiplostim using a Markov model implemented over a lifetime horizon featuring clinically meaningful health states (on treatment, treatment discontinuation, mortality) using clinical trial data for health state transitions. The cost of drugs, routine care, bleeding episodes and adverse events were represented in the model [26]. The total lifetime cost of eltrombopag treatment was estimated at \$1.58 million versus \$2.13 million for romiplostim. Eltrombopag therapy resulted in a gain of 17.58 LYs and 14.68 QALYs over a lifetime time horizon, improvements of 0.06 and 0.01 compared with romiplostim. Eltrombopag was “dominant” in terms of both LYs and QALYs, as it was associated with lower cost and slightly greater benefit than romiplostim. In all probabilistic iterations, the total cost of eltrombopag treatment was lower than with romiplostim, primarily because of lower drug costs.

Anand Dalal

Executive Director, Hematology and CAR-T Franchise Head

US Health Economics and Outcomes Research (HE&OR)

Novartis Pharmaceutical Corporation

## References

1. *Unsupported Price Increase Assessment: Protocol*. April 12, 2021]; Available from: [https://icer.org/wp-content/uploads/2021/04/ICER\\_UPI\\_2021\\_Protocol.pdf](https://icer.org/wp-content/uploads/2021/04/ICER_UPI_2021_Protocol.pdf).
2. Shimano, K.A., et al., *A Phase 3 Study of Eltrombopag Vs. Standard First-Line Management for Newly Diagnosed Immune Thrombocytopenia in Children*. 2019, American Society of Hematology Washington, DC.
3. *A Study to Assess the Ability of Eltrombopag to Induce Sustained Remission in Subjects With ITP (TAPER)*. [cited 2021 October 6, 2021]; NCT03524612:[Available from: <https://clinicaltrials.gov/ct2/show/NCT03524612>.
4. Rodeghiero, F., et al., *Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group*. Blood, The Journal of the American Society of Hematology, 2009. **113**(11): p. 2386-2393.
5. Neunert, C., et al., *American Society of Hematology 2019 guidelines for immune thrombocytopenia*. Blood advances, 2019. **3**(23): p. 3829-3866.
6. Vianello, F., et al., *Thrombopoietin receptor agonists as second-line therapy in splenectomy-eligible persistent immune thrombocytopenia: a case series*. Blood Coagulation & Fibrinolysis, 2019. **30**(6): p. 295-299.
7. Lal, L.S., et al., *Second-line treatments and outcomes for immune thrombocytopenia: A retrospective study with electronic health records*. Research and practice in thrombosis and haemostasis, 2020. **4**(7): p. 1131-1140.
8. Ruiz-Negron, N., et al., *Comparing the Risk of Complications for Second-Line Treatments of Immune Thrombocytopenia in Veterans: A US National Study*. 2019, American Society of Hematology Washington, DC.
9. González-López, T.J., et al., *Use of eltrombopag for patients 65 years old or older with immune thrombocytopenia*. European journal of haematology, 2020. **104**(3): p. 259-270.
10. Moulis G., G.J., Rueter M., Lafaurie M., Comont T., Mahévas M., Viallard J.F., Ebbo M., Audia S., Chèze S., Sommet A., Beyne-Rauzy O., Godeau B., Lapeyre-Mestre M., *Off-label use of eltrombopag in adult patients with immune thrombocytopenia before six months of disease duration in the real-world in France. Results of the ELEXTRA study*. HemaSphere 2021, 2021. **5**(S2).
11. Mishra, K., et al., *Real-world experience of eltrombopag in immune thrombocytopenia*. American journal of blood research, 2020. **10**(5): p. 240.
12. Mingot-Castellano, M.E., et al., *Treatment characteristics, efficacy and safety of thrombopoietin analogues in routine management of primary immune thrombocytopenia*. Blood Coagulation & Fibrinolysis, 2018. **29**(4): p. 374-380.
13. Puavilai, T., et al., *Treatment efficacy for adult persistent immune thrombocytopenia: a systematic review and network meta-analysis*. British journal of haematology, 2020. **188**(3): p. 450-459.
14. Kolanis, S., et al., *Safety and Efficacy of Eltrombopag in Children and Adults with Immune Thrombocytopenia: A Systematic Review and Meta-Analysis*. Cardiovascular & Hematological Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Cardiovascular & Hematological Agents), 2021. **19**(1): p. 83-92.
15. Lucchini, E., et al., *Eltrombopag second-line therapy in adult patients with primary immune thrombocytopenia in an attempt to achieve sustained remission off-treatment: results of a*



- phase II, multicentre, prospective study*. British Journal of Haematology, 2021. **193**(2): p. 386-396.
16. Cooper, N., et al., *Immune thrombocytopenia (ITP) World Impact Survey (I-WISH): Impact of ITP on health-related quality of life*. American journal of hematology, 2021. **96**(2): p. 199-207.
  17. Cooper, N., et al., *Geographic distribution of patient and physician itp treatment preferences and effect of physician caseload on treatment practices: Results from the itp world impact survey (i-wish)*. HemaSphere, 2021: p. 551-551.
  18. Cuker, A., et al., *Tapering thrombopoietin receptor agonists in primary immune thrombocytopenia: Expert consensus based on the RAND/UCLA modified Delphi panel method*. Research and Practice in Thrombosis and Haemostasis, 2021. **5**(1): p. 69-80.
  19. Elbedewy, T.A., et al., *Intermittent versus Daily Eltrombopag Dosage Protocols for the Treatment of Primary Immune Thrombocytopenia: Real-Life Experience*. Journal of Blood Medicine, 2020. **11**: p. 533.
  20. Gonzalez-Lopez, T.J., et al., *Long Term Discontinuation of Eltrombopag after Remission in Primary Immune Thrombocytopenia: 8-Year Follow-up Data from 15 Spanish Centers*. 2019, American Society of Hematology Washington, DC.
  21. Iino, M., Y. Sakamoto, and T. Sato, *Treatment-free remission after thrombopoietin receptor agonist discontinuation in patients with newly diagnosed immune thrombocytopenia: an observational retrospective analysis in real-world clinical practice*. International Journal of Hematology, 2020. **112**: p. 159-168.
  22. Rivolti, E., et al. *EFFICACY, SAFE, SUSTAINED RESPONSE OF TPO-MIMETICS IN NEWLY DIAGNOSED, PERSISTENT, CHRONIC ITP PATIENTS: A SINGLE CENTER EXPERIENCE*. in *HAEMATOLOGICA*. 2019. FERRATA STORTI FOUNDATION VIA GIUSEPPE BELLI 4, 27100 PAVIA, ITALY.
  23. *Data on File. Budget impact analysis of treating chronic immune thrombocytopenia with eltrombopag*. 2020.
  24. Patwardhan, P., et al., *Cost-minimization analysis comparing eltrombopag vs romiplostim for adults with chronic immune thrombocytopenia*. Journal of Managed Care & Specialty Pharmacy, 2021: p. 1-10.
  25. Cai, B., et al., *Healthcare resource use and direct costs in severe aplastic anemia (SAA) patients before and after treatment with eltrombopag*. Journal of medical economics, 2020. **23**(3): p. 243-251.
  26. Tremblay, G., et al., *The cost-effectiveness of eltrombopag for the treatment of immune thrombocytopenia in the United States*. Clinical therapeutics, 2020. **42**(5): p. 860-872. e8.

October 12, 2021

Steven D. Pearson, MD, MSc, FRCP  
President  
Institute for Clinical and Economic Review  
Two Liberty Square, Ninth Floor  
Boston, MA 02109

**Re: 2020 Unsupported Price Increase Report, Preliminary Assessment of CIMZIA, Price Increase Supported by Evidence**

Dear Dr. Pearson,

UCB appreciates the opportunity to comment on ICER's UPI Preliminary Assessment, in which ICER has concluded that the pricing of CIMZIA® (certolizumab pegol) in 2019-2020 was supported by new clinical evidence. UCB firmly believes that the pricing of CIMZIA is well-supported by our overarching clinical development program and the value CIMZIA delivers for patients, which ICER acknowledged in this assessment.

**UCB has continued to invest in developing new clinical evidence for CIMZIA, which, as ICER concludes in its UPI report, supports CIMZIA's pricing during ICER's timeframe for review.**

Given UCB's commitment to patient-centricity and ongoing investment in research and development, we agree with ICER's recognition that the value of CIMZIA is clearly supported by new clinical evidence. CIMZIA is a tumor necrosis factor (TNF) inhibitor with a total of six U.S. Food and Drug Administration (FDA) approved indications for the treatment of chronic autoimmune diseases including: ankylosing spondylitis (AS), rheumatoid arthritis (RA), psoriatic arthritis, plaque psoriasis, Crohn's disease, and, most-recently, non-radiographic axial spondyloarthritis (nr-axSpA). As such, CIMZIA is a meaningful treatment for patients experiencing a variety of severe, chronic autoimmune diseases.

Since CIMZIA was first approved, UCB has continued to generate evidence to discover the potential of CIMZIA for additional patient populations with high unmet need, including those suffering from nr-axSpA. nr-axSpA is a chronic inflammatory condition in which the immune system attacks healthy tissue in the spine and sacroiliac joints (which link the pelvis and the spine). Patients diagnosed with nr-axSpA are faced with significant disease burden, including chronic and often debilitating back pain, stiffness, and fatigue, and receive sub-optimal treatment. Based on results from the C-axSpAnd trial<sup>1</sup>—a Phase III, multi-center, double-blind, placebo-controlled 52-week study in which patients treated with CIMZIA demonstrated major improvement over those given placebo—FDA granted approval of CIMZIA for the treatment of nr-axSpA in March 2019. With this label expansion, CIMZIA became the first FDA-approved treatment for nr-axSpA, and, to date, remains the only TNF inhibitor approved to treat nr-axSpA. UCB agrees with ICER's characterization of the C-axSpAnd study as new, "high-quality evidence of a substantial benefit of treatment with [CIMZIA] for patients with axSpA" and its resultant conclusion that CIMZIA's pricing was supported during the timeframe of ICER's review.



Inspired by **patients.**  
Driven by **science.**

UCB is confident in the value of CIMZIA to patients suffering from severe, chronic autoimmune diseases, and we are pleased that ICER's assessment of our clinical evidence acknowledges that value. UCB is proud of the innovations we have delivered, and we are excited about our promising pipeline that will further our mission of creating value for patients, now and into the future.

Sincerely,

A handwritten signature in black ink, appearing to read 'Patricia A. Fritz'.

Patricia A. Fritz  
Vice President, U.S. Corporate Affairs  
UCB, Inc.  
1950 Lake Park Drive  
Smyrna, GA 30080  
770.970.8585 office  
678.907.5867 mobile  
Patty.Fritz@ucb.com

---

<sup>1</sup> Deodhar A, Gensler LS, Kay J, et al. A fifty-two-week, randomized, placebo-controlled trial of certolizumab pegol in nonradiographic axial spondyloarthritis. *Arthritis & Rheumatology*. 2019;71(7):1101-1111. ([link](#)).