Unsupported Price Increase Report

2019 Assessment

October 8, 2019
(Updated November 6, 2019)

Authors	
David M. Rind, MD, MSc Chief Medical Officer Institute for Clinical and Economic Review	**Eric Borrelli, PharmD, MBA** Evidence Synthesis Intern Institute for Clinical and Economic Review
Foluso Agboola, MBBS, MPH Director, Evidence Synthesis Institute for Clinical and Economic Review	**Steven D. Pearson, MD, MSc** President Institute for Clinical and Economic Review
Varun M. Kumar, MBBS, MPH, MSc (Former) Associate Director of Health Economics Institute for Clinical and Economic Review	

None of the above authors disclosed any conflicts of interest.

DATE OF PUBLICATION: October 8, 2019 (Updated November 6, 2019)

We would also like to thank Laura Cianciolo and Maria M. Lowe for their 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 http://www.icer-review.org.

The funding for this report comes from the Laura and John Arnold Foundation. No funding for this work comes from health insurers, pharmacy benefit managers (PBMs), or life science companies. ICER receives approximately 21% 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 Biogen and Genentech. For a complete list of funders and for more information on ICER's support, please visit http://www.icer-review.org/about/support/.

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

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List of Acronyms Used in this Report

CI	Confidence interval
COBI	Cobicistat
CPI	Consumer price index
EIM	Extraintestinal manifestation
EVG	Elvitegravir
FDA	Food and Drug Administration
FTC	Emtricitabine
HIV	Human immunodeficiency virus
ICER	Institute for Clinical and Economic Review
PrEP	Pre-exposure prophylaxis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RNA	Ribonucleic acid
TAF	Tenofovir alafenamide
TDF	Tenofovir disoproxil fumarate
TNF	Tumor necrosis factor
UPI	Unsupported price increase
US	United States
WAC	Wholesale acquisition cost

Executive Summary

Update (Added November 6, 2019)

After publication of the Unsupported Price Increase Report, Genentech provided ICER with exact values for the net price of Rituxan in Q42016 and Q42018, and the volume sold in 2017 and 2018. Due to the discrepancy between the exact values and the data ICER obtained from SSR Health, LLC, ICER decided to update the report with the data provided by Genentech. As noted in the updated version of this report, over the 24-month period for which price changes were assessed, the net price of Rituxan increased by almost 14%, which results in an estimated increase in drug spending of approximately $549 million. Genentech was the only manufacturer on the list to provide ICER with exact numbers.

In addition, ICER notes that due to the imprecision of volume data for the other assessed drugs, there remains some uncertainty in all other estimates of net price change. As such, small differences in estimated increases in spending across drugs should not be assumed to be meaningful. In particular, the exact ordering of Truvada and Rituxan is uncertain given the estimated similar increases in spending.

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. For example, both California and Vermont now have laws tracking substantial drug price increases, requiring drug manufacturers to submit information that might justify increases above a certain threshold.[1-3] Despite these initiatives, there has 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. For several years, the Institute for Clinical and Economic Review (ICER) has received requests from state policymakers and others to fill this gap, but we had no dedicated funding or specified methodology to do so. Therefore, in 2017 we sought and received funding from the Laura and John Arnold Foundation to develop a new line of ICER reports evaluating selected high-impact drugs with substantial price increases. These new reports seek to identify drugs for which there was no new clinical evidence that could support their price increases. These reports are called Unsupported Price Increase (UPI) reports, and this is the first such report. A detailed description of the entire UPI Protocol is available separately.

We selected drugs to review whose estimated net price increases over a two-year period would have caused the greatest increase in drug spending in the United States (US). Up to three additional drugs could be selected based on nominations received from the public. We obtained a

list of the 100 drugs with the largest sales revenue in calendar year 2018 in the US; this information came from SSR Health, LLC, the health care division of SSR, LLC, an independent investment research firm. We then excluded 23 drugs from this list where the increase in wholesale acquisition cost (WAC) over the two years (eight quarters) from fourth quarter 2016 through fourth quarter 2018 was no larger than twice the increase in medical consumer price increase (CPI) over the same period. For the remaining 77 drugs, we determined, where possible, the increase in spending on these drugs in the US during 2017-18 that was due to increases in net price. From this list of 77, the intent was to select the top 10 drugs for assessment. Under the UPI Protocol, manufacturers submitted information for two drugs showing that they did not belong in the top 10. Based on public input, lenalidomide (Revlimid®) was added to the remaining eight drugs, creating a list of nine drugs for assessment.

The goal of these assessments was to determine whether there was new clinical evidence in the prior three years (2016 through 2018) for the drugs under review. Based either on submissions from manufacturers or an ICER systematic review, ICER reviewed randomized clinical trials, high quality comparative observational studies, and, for low frequency harms, large uncontrolled studies. For drugs with multiple indications, evidence was sought for indications responsible for at least 10% of a drug's utilization. ICER reviewed the quality of the new evidence using the widely-accepted evidence grading system called GRADE.[4] For evidence that was felt to be high or moderate quality, ICER then assessed the magnitude of the additional net clinical benefit compared with what was previously known. Drugs under assessment without evidence meeting these criteria are reported as having price increases "unsupported by new clinical evidence." Drugs found to have moderate/high quality new evidence of a substantial improvement in net health benefit compared with what was previously known are reported as having price increases "with new clinical evidence."

Table ES1 shows the results of the assessments for these nine drugs. Seven were found to have price increases unsupported by new clinical evidence and two were found to have price increases with new clinical evidence. The total increase in spending in the US over two years due to price increases for the seven drugs found to have unsupported price increases amounted to $4.8 billion.

ICER does not have the capacity to perform full economic analyses on the nine 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 cannot determine whether the price increases for the two drugs that had new clinical evidence are justified or meet an ICER value-based 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 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. Assessment Results

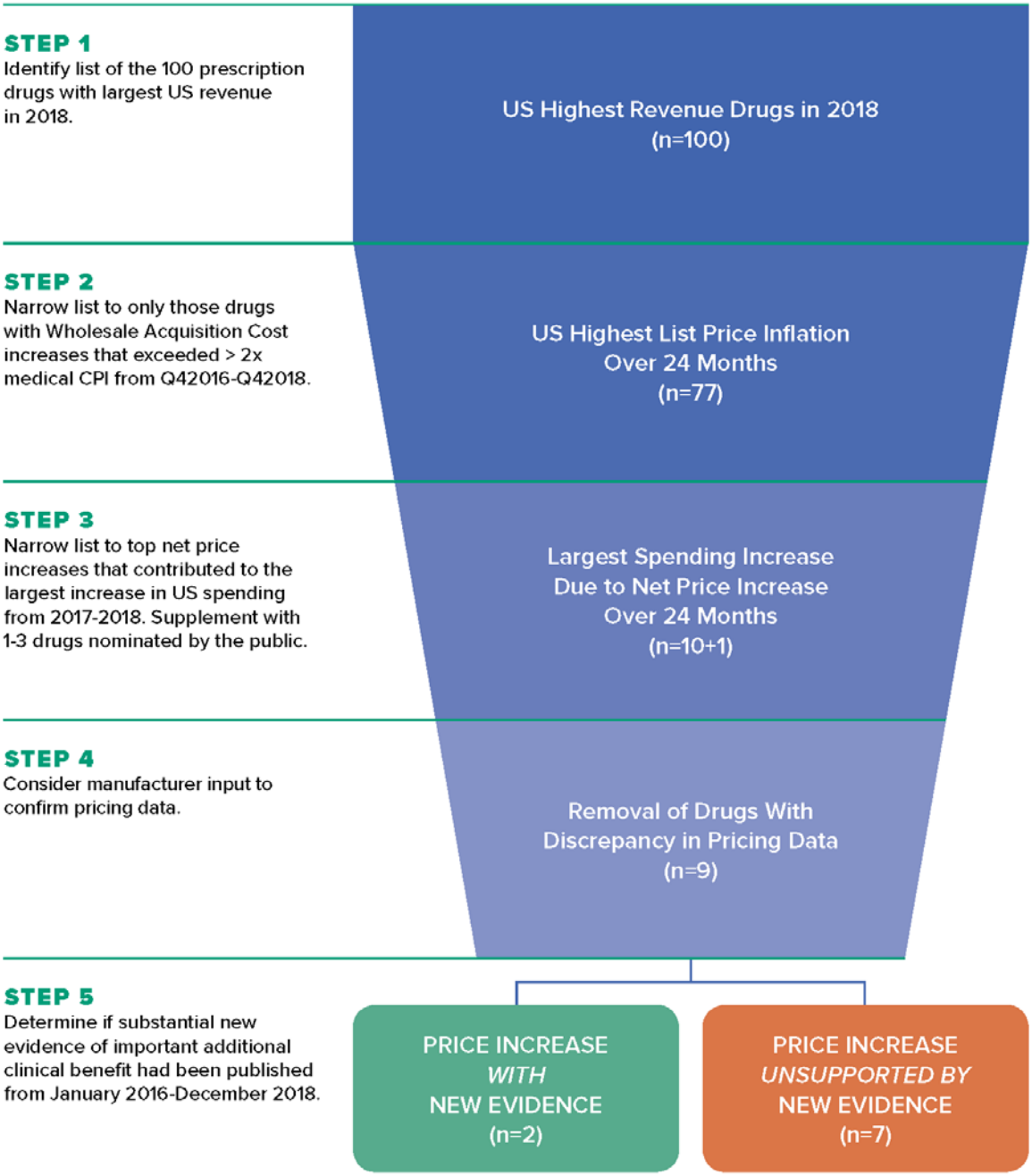
Drug	Q42016 to Q42018 Percentage Change		Increase in Spending Impact Due to Net Price Change (in Millions)
	WAC	Net Price	
Drugs with Price Increases Unsupported by New Clinical Evidence			
Humira® (Adalimumab)	19.1%	15.9%	$1,857
Lyrica® (Pregabalin)	28.3%	22.2%	$688
Truvada® (TDF/FTC)	14.3%	23.1%	$550
Rituxan® (Rituximab)*	17.0%	13.8%	$549
Neulasta® (Pegfilgrastim)	14.6%	13.4%	$489
Cialis® (Tadalafil)	26.2%	32.5%	$403
Tecfidera® (Dimethyl Fumarate)	16.7%	9.8%	$313
Drugs with Price Increases with New Clinical Evidence†			
Genvoya® (EVG/COBI/FTC/TAF)	14.3%	21.7%	$651
Revlimid® (Lenalidomide)	25.8%	--	--

*After publication of the Unsupported Price Increase Report, Genentech provided ICER with exact values for the net price of Rituxan in Q42016 and Q42018, and the volume sold in 2017 and 2018. The updated report reflects the new net price and volume data, which alters the position of Rituxan on the final list.

†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



As anticipated in the UPI Protocol, changes to the UPI procedures were made during this review and the experience of this review will influence changes in the protocol for the next UPI report.

1. Introduction

Update (Added November 6, 2019)

After publication of the Unsupported Price Increase Report, Genentech provided ICER with exact values for the net price of Rituxan in Q42016 and Q42018, and the volume sold in 2017 and 2018. Due to the discrepancy between the exact values and the data ICER obtained from SSR Health, LLC, ICER decided to update the report with the data provided by Genentech. As noted in the updated version of this report, over the 24-month period for which price changes were assessed, the net price of Rituxan increased by almost 14%, which results in an estimated increase in drug spending of approximately $549 million. Genentech was the only manufacturer on the list to provide ICER with exact numbers.

In addition, ICER notes that due to the imprecision of volume data for the other assessed drugs, there remains some uncertainty in all other estimates of net price change. As such, small differences in estimated increases in spending across drugs should not be assumed to be meaningful. In particular, the exact ordering of Truvada and Rituxan is uncertain given the estimated similar increases in spending.

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. For example, both California and Vermont now have laws tracking substantial drug price increases, requiring drug manufacturers to submit information that might justify increases above a certain threshold.[1-3] Despite these initiatives, there has 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. For several years, the Institute for Clinical and Economic Review (ICER) has received requests from state policymakers and others to fill this gap, but we had no dedicated funding or specified methodology to do so. Therefore, in 2017 we sought and received funding from the Laura and John Arnold Foundation to develop a new line of ICER reports evaluating selected high-impact drugs with substantial price increases. These new reports seek to identify drugs for which there was no new clinical evidence that could support their price increases. These reports are called Unsupported Price Increase (UPI) reports, and this is the first such report.

In mid-2018, we organized a multi-stakeholder advisory group to provide input into the design of an approach for these reports. The advisory group was comprised of representatives from patient groups, drugmakers, and insurers representing Medicaid and the private market. Working with this group over several months, ICER developed a UPI Protocol for the reports.

The annual UPI report may evaluate up to 13 drugs that have experienced substantial price increases over a two-year time period. As described in later sections, this year's UPI report evaluated changes in the evidence base for nine drugs and assessed whether there was potential evidentiary support for price increases.

It is important to note that ICER does not have the capacity to perform full economic analyses on the nine 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 value-based price benchmark. Instead, the analyses focused on whether substantial new evidence existed that *could* justify a price increase. By identifying whether there is, or is not, new evidence of improved safety or effectiveness for drugs with substantial price increases we hope to take an important first step in providing the public and policymakers with information they can use to advance the public debate on drug price increases.

2. Selection of Drugs for Review

The ultimate goal of the drug selection process was to identify the top 10 drugs whose estimated net price increases over a two-year period would have caused the greatest increase in drug spending in the United States (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.

We obtained a list of the 100 drugs with the largest sales revenue in calendar year 2018 in the US. This information came from SSR Health, LLC, the health care division of SSR, LLC, an independent investment research firm. Sales revenue data on drugs manufactured by companies that are not publicly traded data were estimated from the Symphony Health dataset, but none were included since they all fell outside the list of top 100 drugs by sales revenue as obtained from the SSR Health database. For each drug, we then determined the change in wholesale acquisition cost (WAC) over an eight quarter (24 month) period using WAC from the SSR Health database. The list of 100 drugs with 2018 sales revenue and the percentage change in WAC from fourth quarter 2016 through fourth quarter 2018 is shown in Table 2.1 on the following page.

Table 2.1. List of Top 100 Drugs with the Highest Sales Revenue (in Millions) in 2018

Drug Name	2018 Sales Revenue	Eight Quarter WAC % Change	Drug Name	2018 Sales Revenue	Eight Quarter WAC % Change	Drug Name	2018 Sales Revenue	Eight Quarter WAC % Change
Humira®	$13,685	19.1%	Copaxone®	$1,711	7.8%	Prezista®/ Prezcobix®	$1,119	16.4%
Revlimid®	$6,469	25.8%	Novolog®/Mix	$1,700	13.3%	Acthar®	$1,110	14.3%
Enbrel®	$4,807	19.0%	Lucentis®	$1,695	-64.3%	Levemir®	$1,091	9.2%
Rituxan®	$4,384	17.0%	Cosentyx®	$1,674	15.9%	Sprycel®	$1,091	14.3%
Opdivo®	$4,239	4.6%	Botox®	$1,639	3.8%	Cimzia®	$1,055	17.8%
Keytruda®	$4,149	5.4%	Mavyret™	$1,599	--	Simponi®/Aria	$1,051	17.2%
Eylea®	$4,077	0.0%	Latuda®	$1,574	20.8%	Rebif®	$1,032	15.4%
Neulasta®	$3,866	14.4%	Vyvanse®	$1,573	--	Jardiance®	$1,028	18.8%
Eliquis®	$3,760	16.5%	Entyvio®	$1,536	17.0%	Tysabri®	$1,025	6.6%
Remicade®	$3,664	4.9%	Prolia®	$1,500	15.2%	Epogen®	$1,010	3.9%
Genvoya®	$3,631	14.3%	Xtandi®	$1,470	16.4%	Shingrix®	$975	--
Lyrica®	$3,594	28.3%	Advair®	$1,459	16.5%	Vimpat®	$969	17.8%
Stelara®	$3,469	15.8%	Sensipar®	$1,436	8.0%	Atripla®	$967	13.9%
Prevnar Family®	$3,360	7.5%	ProQuad®/M-M-R II®/Varivax®	$1,430	9.1%	Orkambi®	$952	5.0%
Tecfidera®	$3,253	16.7%	Fluzone®	$1,425	79.8%	Letairis®	$943	6.9%
Herceptin®	$2,973	12.6%	Avonex®	$1,420	17.8%	Aranesp®	$942	3.7%
Imbruvica®	$2,968	19.0%	Xyrem®	$1,405	16.2%	Yervoy®	$941	4.6%
Avastin®	$2,968	9.8%	Xeljanz®	$1,393	17.2%	Velcade®	$936	0.0%
Ibrance®	$2,921	8.7%	Pomalyst®	$1,391	23.7%	Epclusa®	$934	0.0%
Victoza®	$2,781	16.4%	Jakafi®	$1,387	15.7%	Afinitor®/ Disperz®	$929	20.7%
Truvada®	$2,605	14.3%	Tivicay®	$1,378	16.6%	Creon®	$928	11.9%
Trulicity®	$2,516	17.4%	Aubagio®	$1,364	11.3%	Humulin®/Mix	$910	7.8%
Xarelto®	$2,477	16.5%	Perjeta®	$1,353	12.6%	Mirena®/Skyla®/ Kyleena®	$889	5.9%
Triumeq®	$2,221	16.6%	Xgeva®	$1,338	8.9%	Actemra®	$875	20.2%
Ocrevus®	$2,123	--	Otezla®	$1,275	27.5%	Tagrisso®	$869	8.1%
Januvia®	$1,969	17.8%	Activase®/ TNKase®	$1,259	8.0%	Symbicort®	$862	12.9%
Xolair®	$1,953	10.3%	Odefsey®	$1,242	14.3%	Spinraza®	$854	--
Lantus®	$1,908	8.5%	Descovy®	$1,217	14.3%	Chantix®	$838	26.7%
Orencia®	$1,875	13.3%	Darzalex®	$1,203	10.2%	Tresiba®	$821	9.2%
Gardasil®/9	$1,872	5.7%	Restasis®	$1,197	19.5%	Sandostatin®/ LAR	$817	15.4%
Invega® Sustenna/ Trinza®	$1,791	14.7%	Xifaxan®	$1,195	13.6%	Janumet®/XR	$811	17.8%
Humalog®/Mix	$1,788	7.8%	Biktarvy®	$1,144	--	Tasigna®	$806	20.7%
Zytiga®	$1,771	18.6%	Alimta®	$1,131	6.9%			
Gilenya®	$1,765	16.5%	Cialis®	$1,129	26.2%			

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 twice medical CPI, the drugs where WAC was unavailable still would not have been included in the list of drugs to be assessed.

We compared these percentage increases in WAC to the increase in the medical care consumer price index (CPI) over the same period and excluded those drugs with a WAC increase that was not greater than 7.32%, which is two times the increase in medical care CPI over this period. The medical care CPI is one of eight major components of the CPI recorded and reported by the US Bureau of Labor Statistics.[5] Medical care CPI comprises medical care services (professional services, hospital and related services, and health insurance) and medical care commodities (medical drugs, equipment, and supplies).[6] Our intent in choosing the overall medical care CPI and not its subcomponents was to reflect increases in drug prices relative to inflation in the overall price of medical care. The 77 drugs shown in Table 2.2 on the following page had an increase in WAC greater 7.32% over the two-year period; the other 23 drugs were excluded from further analysis.

For these 77 drugs, we examined the estimated net price change per unit of drug sold over the same eight quarters (fourth quarter 2016 to fourth quarter 2018), adjusting for different dosing strengths where applicable. To estimate a net price per unit, SSR Health combines available data on unit sales with data published in manufacturers' earnings reports on US sales revenue for each drug. These revenue numbers are net of discounts, rebates, concessions to wholesalers and distributors, and patient assistance programs. The impact of net price increases on overall drug spending during the two-year period from 2017 through 2018 was calculated by multiplying the net price change for each drug by the average estimated number of units sold in calendar years 2017 and 2018.

Table 2.2 is ordered by change in drug spending and gives this figure for 61 of the 77 drugs. Because of lack of face validity, we do not show the change in drug spending for 14 drugs that had a net price higher than WAC price in at least one of the eight quarters in which data were captured. These discrepancies occurred because of difficulties in estimating unit volume numbers for these drugs. As such, we were unable to assess the position of these 14 drugs in the list and they appear at the end. Based on manufacturer input providing revised figures on change in net price and volume, the change in spending is also not shown for two additional drugs (see footnotes in Table 2.2).

Table 2.2. Drugs with WAC Percentage Change Greater Than Twice Medical Care CPI

Drug Name	Increase in Spending Due to Net Price Change*	Drug Name	Increase in Spending Due to Net Price Change*	Drug Name	Increase in Spending Due to Net Price Change*
Humira	$1,857	Humulin/Mix	$107	Janumet/XR	($352)
Lyrica	$688	Otezla	$106	Januvia	($377)
Genvoya	$651	Perjeta	$105	Symbicort	($389)
Truvada	$550	Xgeva	$99	Stelara	($458)
Rituxan	$549†	Vimpat	$97	Levemir	($534)
Neulasta	$489	Xifaxan	$75	Novolog/Mix	($574)
Avonex	‡	Herceptin	$70	Tresiba	($702)
Cialis	$403	Actemra	$61	Xarelto	($710)
Enbrel	§	Rebif	$52	Copaxone	($918)
Tecfidera	$313	Tagrisso	$48	Advair	($1,011)
Tasigna	$312	Cimzia	$40	Lantus	($1,267)
Xtandi	$296	Creon	($1)	Ibrance	#
Imbruvica	$245	Zytiga	($15)	Entyvio	#
Latuda	$232	Darzalex	($16)	ProQuad/M-M-R II/Varivax	#
Prolia	$222	Tivicay	($17)	Xyrem	#
Atripla	$221	Sandostatin/ LAR	($39)	Revlimid	#
Victoza	$207	Activase/ TNKase	($43)	Sensipar	#
Chantix	$206	Sprycel	($70)	Avastin	#
Odefsey	$203	Triumeq	($79)	Pomalyst	#
Descovy	$198	Simponi/Aria	($106)	Acthar	#
Xolair	$183	Xeljanz	($123)	Prevnar Family	#
Afinitor/Disperz	$177	Trulicity	($125)	Jakafi	#
Aubagio	$162	Jardiance	($204)	Fluzone	#
Prezista/ Prezcobix	$133	Cosentyx	($208)	Orencia	#
Gilenya	$114	Eliquis	($222)	Invega Sustenna/ Trinza	#
Humalog/Mix	$107	Restasis	($267)		

*In millions.

†Exact value provided by Genentech.

‡Biogen provided information that the net price increase of Avonex was lower than what SSR Health reported such that the increase in spending would place it lower than the fifteenth position on this list. Per the UPI Protocol, a corrected position below 15 removes a drug from the assessment.

§Amgen provided information that the net price of Enbrel decreased over Q42016-Q42018.

#Because of lack of face validity, we do not show the change in drug spending for 14 drugs that had a net price higher than WAC price in at least one of the eight quarters in which data were captured.

Table 2.3 shows the nine drugs that were chosen for assessment. This includes the top eight drugs in Table 2.2 based on increase in drug spending (initially the top 10 drugs prior to manufacturer input on two drugs as discussed above). The UPI process allowed for up to three additional drugs to be reviewed based on public input. We received feedback that lenalidomide (Revlimid) had experienced large price increases causing public concern. Lenalidomide was one of the 14 drugs where the net price numbers when compared with WAC lacked face validity for at least one quarter, and so we were unable to assess the true change in net price or spending for lenalidomide, however we chose to add it to the assessment as a drug of public concern.

We did not add any other drugs, and so Table 2.3 includes eight drugs based on changes in drug spending and one drug based on public concern. The table also shows the percentage change in WAC for these drugs, and, for the eight drugs where it could be estimated, the percentage change in net price over the two-year period from the fourth quarter of 2016 to the fourth quarter of 2018, and the and the increase in drug spending during calendar years 2017 and 2018.

Table 2.3. Drugs Selected for Assessment

Rank	Drug	Q42016 to Q42018 Percentage Change		Increase in Drug Spending Due to Net Price Change (in Millions)
		WAC	Net Price	
1	Humira (Adalimumab)	19.1%	15.9%	$1,857
2	Lyrica (Pregabalin)	28.3%	22.2%	$688
3	Genvoya (EVG/COBI/FTC/TAF)	14.3%	21.7%	$651
4	Truvada (TDF/FTC)	14.3%	23.1%	$550
5	Rituxan (Rituximab)*	17%	13.8%	$549
6	Neulasta (Pegfilgrastim)	14.6%	13.4%	$489
7	Cialis (Tadalafil)	26.2%	32.5%	$403
8	Tecfidera (Dimethyl Fumarate)	16.7%	9.8%	$313
--	Revlimid (Lenalidomide)	25.8%	--	--

*After publication of the Unsupported Price Increase Report, Genentech provided ICER with exact values for the net price of Rituxan in Q42016 and Q42018, and the volume sold in 2017 and 2018. The updated report reflects the new net price and volume data, which alters the position of Rituxan on the final list.

3. Assessments

The goal of these assessments was to determine whether there was new clinical evidence in the prior three years (2016 through 2018) for the drugs under review. Based either on submissions from manufacturers or an ICER systematic review, ICER reviewed randomized clinical trials, high quality comparative observational studies, and, for low frequency harms, large uncontrolled studies. For drugs with multiple indications, evidence was sought for indications responsible for at least 10% of a drug's utilization. ICER reviewed the quality of the new evidence using the widely accepted evidence grading system called GRADE.[4] For evidence that was felt to be high or moderate quality, ICER then assessed the magnitude of the additional net clinical benefit compared with what was previously known. Drugs under assessment without evidence meeting these criteria are reported as having price increases "unsupported by new clinical evidence." Drugs found to have moderate/high quality new evidence of a substantial improvement in net health benefit compared with what was previously known are reported as having price increases "with new clinical evidence." A detailed description of the entire UPI Protocol is available separately.

3.1 Humira (Adalimumab)

Introduction

Humira (adalimumab, AbbVie Inc.) is a humanized monoclonal antibody that binds specifically to tumor necrosis factor (TNF).[7] It was approved by the FDA in 2002, and it is indicated for the treatment of 10 different chronic diseases: rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, adult and pediatric Crohn's disease, ulcerative colitis, plaque psoriasis, adult and adolescent hidradenitis suppurativa, and adult and pediatric non-infectious uveitis.[7]

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
- Ulcerative colitis
- Plaque psoriasis

Price Increase

Over the 24-month (eight quarters) period for which price changes were assessed, adalimumab's WAC increased by approximately 19%, while its net price increased by almost 16%. Considering the average volume sold in 2017-18, this net price change over the assessed eight quarters resulted in an estimated increase in drug spending of $1.86 billion.

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 2016.[7] The manufacturer submitted 204 references (160 conference presentations and 44 published manuscripts) as new clinical information (published between January 1, 2016 and December 31, 2018) to be considered for our review. However, none met our inclusion criteria of *new* information on benefits and/or harms within the indications that account for greater than 10% of use.

The primary reasons for exclusion are provided in Table 3.1 (Appendix A provides more information on each study). As an example, we highlight below one of the trials that was submitted and our rationale for excluding the trial. We did not conduct an additional search for new clinical evidence.

Table 3.1. Reasons for Exclusion

Reasons for Exclusion	Number of References
Indication accounts for less than 10% of use (e.g., nail psoriasis)	2
Previously known information about adalimumab (e.g., efficacy of adalimumab vs. placebo in plaque psoriasis)	28
Adalimumab in all comparison arms	6
Intervention/comparison outside our scope (TNF inhibitors vs. non-TNF inhibitors)	62
Outcomes not relevant to our scope (e.g., cost-effectiveness analysis)	25
Study design does not meet our criteria for assessing efficacy (e.g., single-arm study)	76
Abstract – limited information on study design	5

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

Example of Excluded Evidence

In **Louis 2018,** data on extraintestinal manifestations (EIM) were pooled from 11 induction, maintenance, and open-label extension studies of adalimumab conducted in patients with Crohn's disease.[8] The median time to initial EIM resolution and first EIM recurrence was calculated. A Cox model was used to determine predictors of initial and durable EIM resolutions. The study found a

significantly greater proportion of EIM resolution in the adalimumab group compared to those on placebo at six months (54% vs. 31%; p<0.001) and at one year (60% vs. 42%; p=0.008). The median time to initial resolution of any EIM was significantly shorter in the adalimumab group compared to placebo. Similarly, among patients who achieved resolution, median time to first EIM recurrence was significantly longer for the adalimumab group versus the placebo group, reflecting a more durable resolution.

Reason(s) for exclusion: This is a pooled analysis of studies that were published in 2013 or earlier. This study does not meet our study design criteria for assessing improved clinical outcome. Furthermore, the study is consistent with what was previously known about adalimumab.

Conclusion

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

3.2 Lyrica (Pregabalin)

Introduction

Lyrica (pregabalin, Pfizer Inc.) is an oral anticonvulsant and analgesic medication that was first approved by the FDA in 2004.[12] It is specifically indicated to be used for the treatment of neuropathic pain associated with diabetic peripheral neuropathy, neuropathic pain associated with spinal cord injury postherpetic neuralgia, adjunctive therapy for the treatment of partial-onset seizures in patients one month of age and older, and fibromyalgia.[12]

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

- Neuropathic pain associated with diabetic peripheral neuropathy
- Adjunctive therapy for the treatment of partial-onset seizures

Price Increase

Over the 24-month (eight quarters) period for which price changes were assessed, pregabalin's WAC increased by approximately 28%, while its net price increased by approximately 22%. Considering the average volume sold in 2017-18, this net price change over the assessed eight quarters resulted in an estimated increase in drug spending of $688 million.

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 pregabalin as of January 2016. The manufacturer did not submit any information to be considered for our review. We conducted an independent systematic literature review to look for new information over the 36 months review timeframe (January 1, 2016 to December 31, 2018) on benefits and harms of pregabalin. Each search was limited to English language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. The search strategies included a combination of indexing terms, as well as free-text terms, and are presented in Appendix Table B1. Subsequent to the literature search and removal of duplicate citations, references went through two levels of screening at both the abstract and full-text levels by two reviewers.

Our literature search identified 608 potentially relevant references, none of which met our inclusion criteria of *new* information on benefits and/or harms of pregabalin (PRISMA flow chart is provided in Appendix Figure B1). The primary reasons for exclusion included study design that does not meet our criteria for assessing efficacy (e.g., single-arm study), outcomes not relevant to the scope of review (e.g., pharmacokinetics of pregabalin), and previously known information about pregabalin.

Conclusion

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

3.3 Genvoya (Elvitegravir, Cobicistat, Emtricitabine, Tenofovir)

Introduction

Genvoya (Gilead Sciences, Inc.) is a once-daily, single-tablet regimen that combines tenofovir alafenamide 10 mg (TAF) with elvitegravir 150 mg (EVG), cobicistat 150 mg (COBI), and emtricitabine 200 mg (FTC). EVG/COBI/FTC/TAF was approved by the FDA on November 5, 2015 for the treatment of human immunodeficiency virus (HIV)-1 in adults and pediatric patients ages 12 years and older who have no antiretroviral treatment history (antiretroviral naïve), and to replace the current antiretroviral regimen in virologically suppressed patients (HIV-1 ribonucleic acid [RNA] less than 50 copies per mL).[13] Based on clinical input, both indications account for greater than 10% of use.

Price Increase

Over the 24-month (eight quarters) period for which price changes were assessed, EVG/COBI/FTC/TAF's WAC increased by approximately 14%, while its net price increased by almost

22%. Considering the average volume sold in 2017-18, this net price change over the assessed eight quarters resulted in an estimated increase in drug spending of $651 million.

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 EVG/COBI/FTC/TAF combination as of January 2016.[13] Twelve references (eight conference presentations and four published manuscripts) were submitted by the manufacturer as new clinical information (published between January 1, 2016 and December 31, 2018) to be considered in the review. However, only two of these studies (Arribas 2017 and DeJesus 2018) met our inclusion criteria of *new* information on benefits and/or harms within the indications stated above. The primary reasons for exclusion are provided in Table 3.2 (Appendix C provides more information on each study). We did not conduct an additional search for new clinical evidence.

Table 3.2. Reasons for Exclusion

Reasons for Exclusion	Number of References
Previously known information (e.g., TAF better on bone health)	3
Outcomes not relevant to our scope (e.g., cost-consequence analysis)	4
Indication accounts for less than 10% of use	1
Study design does not meet our criteria for assessing efficacy (e.g., single-arm study)	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 3.3. Summary of Clinical Evidence Identified

Baseline Evidence	Included Evidence
Evidence from two randomized controlled trials showed that in antiretroviral naïve adults, EVG/COBI/FTC/TAF was not significantly different from EVG/COBI/FTC/tenofovir disoproxil fumarate (TDF) (TDF combination) in virologic efficacy at 48 weeks.[13,14]	Arribas 2017: Longer-term data from two randomized controlled trials showed that EVG/COBI/FTC/TAF was superior to TDF combination at 144 weeks in antiretroviral naïve adults.[15]
Evidence from one randomized controlled trial showed that in virologically suppressed adults, there was no statistically significant difference between continuing pre-existing TDF combination (FTC/TDF + a third) and switching to EVG/COBI/FTC/TAF at 48 weeks.[13,16]	DeJesus 2018: Longer-term data from one randomized controlled trial showed that switching to EVG/COBI/FTC/TAF was superior to TDF combination at 96 weeks in virologically-suppressed adults.[17]

Included Evidence

Arribas 2017 evaluated the efficacy and safety of EVG/COBI/FTC/TAF in antiretroviral naïve adults in two multicentered Phase III randomized controlled trials (n=1,733) at 144 weeks. Patients were randomized 1:1 to once-daily TAF 10 mg (n=866) versus TDF 300 mg (n=867), both co-formulated with elvitegravir, cobicistat, emtricitabine. At 144 weeks, the pre-specified pooled analysis of the two trials showed that EVG/COBI/FTC/TAF was superior to the TDF regimen in virologic efficacy (84.2% vs. 80.0% had HIV-1 RNA <50 copies/mL [difference 4.2%; 95% CI: 0.6% to 7.8%]). Consistent with what was already known, EVG/COBI/FTC/TAF was less harmful than the TDF combination on bone and renal health, consequently leading to a lower rate of discontinuation (1.3% vs. 3.3%; p=0.006).[15]

DeJesus 2018 evaluated the efficacy and safety of EVG/COBI/FTC/TAF in virologically-suppressed adults in a Phase III, multicentered, open-label, active-controlled trial at 96 weeks. Patients were randomized 2:1 to receive either EVG/COBI/FTC/TAF (n=959) or to continue one of four TDF-containing combinations (TDF combination) (n=477). At 96 weeks, EVG/COBI/FTC/TAF was superior to TDF in virologic efficacy (93% vs. 89% had HIV-1 RNA <50 copies/mL [difference 3.7%; 95% CI: 0.4% to 7.0%]).[17]

Rating of Included Evidence (Quality and Magnitude)

Other than uncertainty caused by imprecision, these randomized controlled trials represent high quality evidence assessing the relative viral suppression of TAF-containing (EVG/COBI/FTC/TAF) and TDF-containing regimens. Prior to these trials, it was believed that TAF and TDF regimens achieved similar viral suppression, so any additional viral suppression by TAF compared with TDF would be added "net" health benefit.

The Arribas 2017 trial provides the most direct comparison of regimens, and the additional viral suppression was 4.2% with a 95% CI of 0.6% to 7.8%. At the lower end of this CI, the added benefit would be at most "incremental." ICER judges that at the upper end of this CI, the added benefit would be "substantial." At the point estimate of 4.2%, ICER judges that this added benefit is also "substantial," although there could be disagreement about this assessment.

We conclude that the new evidence provides high certainty of an incremental benefit for EVG/COBI/FTC/TAF compared with what was previously known, and moderate certainty of a substantial benefit with downgrading of certainty for imprecision.

Conclusion

After careful review of the evidence, we conclude that EVG/COBI/FTC/TAF (Genvoya) had a price increase *with* new clinical evidence.

3.4 Truvada (Emtricitabine/Tenofovir Disoproxil Fumarate)

Introduction

Truvada (Gilead Sciences, Inc.) is a fixed dose regimen that combines two antiretroviral medications: TDF and FTC. TDF/FTC was first approved by the FDA on August 2, 2004 to be used in combination with other antiretroviral agents for the treatment of HIV-infected adults and children ages 12 years and older.[18] It was subsequently approved on July 16, 2012 for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk, and the label was most recently expanded on May 15, 2018 to allow use for PrEP in adolescents at high risk.[18] Based on clinical input, both indications (treatment of HIV and PrEP) account for greater than 10% of use.

Price Increase

Over the 24-month (eight quarters) period for which price changes were assessed, TDF/FTC's WAC increased by approximately 14%, while its net price increased by 23%. Considering the average volume sold in 2017-18, this net price change over the assessed eight quarters resulted in an estimated increase in drug spending of $550 million.

Review of Clinical Evidence

We reviewed the safety and clinical effectiveness information provided in the FDA label and related published literature to assess the baseline evidence on TDF/FTC. Eleven references (seven conference presentations and four published manuscripts) were submitted by the manufacturer as new clinical information (published between January 1, 2016 and December 31, 2018) to be considered for our review but none met our inclusion criteria of *new* information on benefits and/or harms within the indications listed above. The primary reasons for exclusion are provided in Table 3.4 (Appendix D provides more information on each study). Of note, none of the studies submitted was a randomized trial or high-quality observational study. As an example, we highlight below one of the trials that was submitted and our rationale for excluding the it. We did not conduct an additional search for new clinical evidence.

Table 3.4. Reasons for Exclusion

Reasons for Exclusion	Number of References
Study design does not meet our criteria for assessing efficacy (e.g., mathematical model of HIV transmission if Centers for Disease Control and Prevention PrEP guidelines were implemented)	5
Outcomes not relevant to scope of review (e.g., cost-effectiveness analysis)	6

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

Example of Excluded Evidence

Jenness 2016 used a mathematical model of HIV transmission dynamics in an open population of men who have sex with men in the US to estimate the proportion of infections that will be averted, and the number needed to treat with PrEP to prevent one new infection under the Centers for Disease Control and Prevention's PrEP guideline.[19] The model predicted that at 40% coverage among men who have sex with men over the next 10 years, the implementation of Centers for Disease Control and Prevention guidelines would prevent 1,162 infections per 100,000 person-years (33% of expected infections) and would require treating 25 uninfected men who have sex with men for one year per infection averted (number needed to treat=25).[19]

Reason(s) for exclusion: This study design does not meet our criteria for assessing improved clinical outcome. As stated in the UPI Protocol, we are looking for new clinical evidence on TDF/FTC over the prior 36 months from randomized trials, high-quality observational studies, or large uncontrolled studies (in cases of low frequency harms) that demonstrates improved clinical or economic outcomes.

Conclusion

After careful review of the evidence submitted by the manufacturer, we conclude that TDF/FTC (Truvada) had a price increase *unsupported* by new clinical evidence.

3.5 Rituxan (Rituximab)

Introduction

Rituxan (rituximab, Genentech Inc.) is a human/mouse chimeric anti-CD20 monoclonal antibody. It was first approved by the FDA in 1997 for non-Hodgkin's lymphoma, and has since gained approval for five other indications: chronic lymphocytic leukemia, rheumatoid arthritis, pemphigus vulgaris, granulomatosis with polyangiitis, and microscopic polyangiitis.[9] Based on the information provided by the manufacturer, the indications that account for greater than 10% of rituximab's use include:

- Non-Hodgkin's lymphoma
    - Follicular lymphoma: used for initial treatment in combination with chemotherapy or as a single agent for maintenance therapy
    - Diffuse large B-cell lymphoma: used in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone or other anthracycline-based chemotherapy regimens
- Chronic lymphocytic leukemia: used in combination with fludarabine and cyclophosphamide for previously untreated and previously treated CD20-positive chronic lymphocytic leukemia in combination with fludarabine and cyclophosphamide
- Rheumatoid arthritis: used in combination with methotrexate in adult patients with moderately-to-severely active rheumatoid arthritis who have inadequate response to one or more TNF inhibitors

Price Increase

Over the 24-month (eight quarters) period for which price changes were assessed, rituximab's WAC increased by approximately 17%, while its net price increased by almost 14%. Considering the average volume sold in 2017-18, this net price change over the assessed eight quarters resulted in an increase in drug spending of $549 million. This number is not an estimate and was provided by the manufacturer.

Review of Clinical Evidence

We reviewed the safety and clinical effectiveness information provided in the FDA label as well as related published literature to assess the baseline evidence on rituximab as of January 2016. The manufacturer submitted 143 references (65 conference presentations and 78 published manuscripts) as new clinical information (published between January 1, 2016 and December 31, 2018) to be considered for our review. However, none met our inclusion criteria of *new* information on benefits and/or harms within the indications that account for greater than 10% of use.

The primary reasons for exclusion are provided in Table 3.5 on the following page (Appendix E provides more information on each study). As an example, we highlight below two of the trials that were submitted and our rationale for excluding them. We did not conduct an additional search for new clinical evidence.

Table 3.5. Reasons for Exclusion

Reasons for Exclusion	Number of References
Indication accounts for less than 10% of use (e.g., pemphigus vulgaris)	3
Previously known information about rituximab related to efficacy (e.g., rituximab was superior to placebo in preventing joint erosion in patients with rheumatoid arthritis who have inadequate response to methotrexate)	16
Previously known information about rituximab related to safety (e.g., serious infection)	9
Rituximab in all comparison arms (e.g., rituximab + lenalidomide vs. rituximab + chemotherapy)	38
New evidence of no clinical improvement with rituximab (e.g., no difference between rituximab plus ibrutinib vs. ibrutinib alone)	11
Intervention/comparison not relevant to scope (e.g., non-TNF targeted biologic vs. anti-TNF that differed from previous treatment)	9
Abstract – limited information on study design	3
Study design does not meet our criteria for assessing efficacy (e.g., single-arm study)	49
Study population outside approved label indication (patients naïve to biologic treatment)	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.

Examples of Excluded Evidence

Joly 2017 was an open-label, randomized trial that compared rituximab plus low-dose prednisone with high-dose prednisone alone in adults with newly diagnosed pemphigus (n=91).[10] Patients were randomly assigned 1:1 to receive either intravenous rituximab (1000 mg on days 0 and 14, and 500 mg at months 12 and 18) plus oral prednisone (0.5 or 1 mg/kg per day) tapered over three or six months (rituximab plus low-dose prednisone group) or oral prednisone alone (1 or 1.5 mg/kg per day) tapered over 12 or 18 months (high-dose prednisone group). At 24 months, 89% of patients on rituximab plus low-dose prednisone achieved complete remission compared with 34% in the high-dose prednisone group (relative risk of success 2.61, 95% confidence interval [CI] 1.71–3.99, p<0.0001). Additionally, patients treated with rituximab experienced fewer severe adverse events.

Reason(s) for exclusion: Although this trial might qualify as evidence of a new benefit, pemphigus accounts for less than 10% of overall utilization of rituximab. As such, we would not consider this as new evidence to support a price increase.

Porter 2016 was an open-label, randomized non-inferiority trial that compared the efficacy and safety of rituximab to TNF inhibitors in patients with active rheumatoid arthritis who have inadequate response to synthetic disease modifying anti-rheumatic drugs, and were naïve to biologic treatment.[11] Patients were randomly assigned 1:1 to rituximab (n=144) or TNF inhibitor (adalimumab or etanercept, n=151). At 12 months, rituximab was shown to be non-inferior to TNF inhibitor on disease activity as assessed by the Disease Activity Score 28-erythrocyte sedimentation rate (-2.6 vs. -2.4; pre-defined non-inferiority margin – 0.19; 95% CI –0.51 to 0.13). Patients treated with rituximab experienced fewer severe adverse events. Additionally, there was no significant difference between the two regimens in terms of health-related quality of life and serious adverse events.

Reason(s) for exclusion: This trial was the first head-to-head trial between rituximab and TNF inhibitors in patients with rheumatoid arthritis naïve to biologic treatments, however, it is outside the labeled indication of "adult patients with moderately-to-severely active rheumatoid arthritis *who have inadequate response to one or more TNF antagonist therapies.*" As such, we would not consider this as new evidence to support a price increase.

Conclusion

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

3.6 Neulasta (Pegfilgrastim)

Introduction

Neulasta (pegfilgrastim, Amgen Inc.) is a leukocyte growth factor that was first approved by the FDA in 2002.[20] Pegfilgrastim is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia, and to increase survival in patients acutely exposed to myelosuppressive doses of radiation.[20] Based on clinical input, only the first indication accounts for greater than 10% of use.

Price Increase

Over the 24-month (eight quarters) period for which price changes were assessed, pegfilgrastim's WAC increased by almost 15%, while its net price increased by about 13%. Considering the average volume sold in 2017-18, this net price change over the assessed eight quarters resulted in an estimated increase in drug spending of $489 million.

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 pegfilgrastim as of January 2016. The manufacturer submitted 12 references (one conference presentation and 11 published manuscripts) as new clinical information (published between January 1, 2016 and December 31, 2018) to be considered for our review but none of them met our inclusion criteria of *new* information on benefits and/or harms within the indications that account for greater than 10% of use.

The primary reasons for exclusion are provided in Table 3.6 (Appendix F provides more information on each study). Of note, none of the studies submitted was a randomized trial. As an example, we highlight below one of the trials that was submitted and our rationale for excluding the trial. We did not conduct an additional search for new clinical evidence.

Table 3.6. Reasons for Exclusion

Reasons for Exclusion	Number of References
Intervention/comparison outside of scope of assessing new evidence on efficacy and/or harms of pegfilgrastim (e.g., same-day vs. next-day pegfilgrastim for febrile neutropenia)	7
Outcomes not relevant to scope of review (e.g., review of cost-effectiveness, physician preferences)	4
Wrong population (i.e., healthy population)	1

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

Example of Excluded Evidence

Weycker 2017 is a retrospective claims database study that compared the risk of febrile neutropenia in patients who received pegfilgrastim prophylaxis on the last day of chemotherapy ("day 0") or 4-5 days following chemotherapy ("days 4-5") with 1-3 days following chemotherapy ("days 1-3," recommended in US practice guideline).[21] In 9% of the chemotherapy cycle where pegfilgrastim prophylaxis was used, patients received pegfilgrastim prophylaxis on days not recommended by the practice guideline (day 0 and days 4-5). Using generalized estimating equations, the odds of febrile neutropenia was significantly higher among patients receiving pegfilgrastim prophylaxis on days not recommended by the practice guideline (day 0 and days 4-5).

Reason(s) for exclusion: This study evaluated the benefit of adhering to the guideline in using pegfilgrastim. It does not provide any evidence related to improved clinical or economic outcome, or provide evidence relating to comparator therapies. As stated in our UPI Protocol, we are looking for new clinical evidence on pegfilgrastim from randomized trials, high-quality observational

studies, or large uncontrolled studies (in cases of low frequency harms) that demonstrate improved clinical and economic outcomes.

Conclusion

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

3.7 Cialis (Tadalafil)

Introduction

Cialis (tadalafil, Eli Lilly and Company) is an oral medication that inhibits the phosphodiesterase type 5 enzyme.[22] It was first approved in 2003 for the treatment of erectile dysfunction. It later received an indication for the treatment of signs and symptoms of benign prostatic hyperplasia.[22] Based on clinical input, both indications account for greater than 10% of use.

Price Increase

Over the 24-month (eight quarters) period for which price changes were assessed, tadalafil's WAC increased by approximately 26%, while its net price increased by approximately 33%. Considering the average volume sold in 2017-18, this net price change over the assessed eight quarters resulted in an estimated increase in drug spending of $403 million.

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 tadalafil as of January 2016. The manufacturer did not submit any information to be considered for our review. We conducted an independent systematic literature review to look for new information over the 36 months review timeframe (January 1, 2016 to December 31, 2018) on benefits and harms of tadalafil. Each search was limited to English language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. The search strategies included a combination of indexing terms, as well as free-text terms, and are presented in Appendix Table G1. Subsequent to the literature search and removal of duplicate citations, references went through two levels of screening at both the abstract and full-text levels by two reviewers.

Our literature search identified 317 potentially relevant references, none of which met our inclusion criteria of *new* information on benefits and/or harms of tadalafil (PRISMA flow chart is provided in Appendix Figure G1). The primary reasons for exclusion included study design that did not meet our criteria for assessing efficacy (e.g., single-arm study, low-quality observational study), study

outside of approved indication (e.g., medical expulsive therapy for urethral stone, treatment of Duchenne and Becker muscular dystrophies), and previously known information about tadalafil (e.g., efficacy of tadalafil plus tamsulosin vs. tamsulosin alone in patients with symptoms of benign prostatic hyperplasia).

Conclusion

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

3.8 Tecfidera (Dimethyl Fumarate)

Introduction

Tecfidera (dimethyl fumarate, Biogen Inc.) was approved by the FDA in March 2013 as an oral disease-modifying agent for relapsing forms of multiple sclerosis.[23]

Price Increase

Over the 24-month (eight quarters) period for which price changes were assessed, dimethyl fumarate's WAC increased by approximately 17%, while its net price increased by almost 10%. Considering the average volume sold in 2017-18, this net price change over the assessed eight quarters resulted in an estimated increase in drug spending of $313 million.

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 dimethyl fumarate as of January 2016. Twenty-nine references (12 conference presentations and 17 published manuscripts) were submitted by the manufacturer as new clinical information (published between January 1, 2016 and December 31, 2018) to be considered for our review. Of the 29, we included one high-quality observational study for further review that potentially met our criteria of *new* information on benefits and/or harms.

The primary reasons for exclusion are provided in Table 3.7 (Appendix H provides more information on each study). Of note, none of the studies submitted was a randomized trial. We did not conduct an additional search for new clinical evidence.

Table 3.7. Reasons for Exclusion

Reasons for Exclusion	Number of References
Study design does not meet our criteria for assessing efficacy (e.g., indirect comparison, low-quality observational trial)	19
Study showing previously known information about dimethyl fumarate	7
Study published outside of the timeframe of our review (2019)	2

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

Table 3.8. Summary of Clinical Evidence Identified

Baseline Evidence	Included Evidence
The efficacy and safety of dimethyl fumarate were demonstrated in two placebo-controlled studies conducted in patients with relapsing-remitting multiple sclerosis**.** There are no head-to-head randomized controlled trials of dimethyl fumarate and other commonly used disease-modifying therapies in multiple sclerosis.[23]	**Braune 2018** evaluated the comparative effectiveness of dimethyl fumarate and other disease-modifying therapies.[24] The authors stated that the results from this study support previously known information about dimethyl fumarate and its comparators. We would have considered this to be a reason to exclude, but we chose to further consider this study for review because the previous knowledge cited by the authors was all based on studies that were published within our timeframe of review (2016-18). However, none of these studies met our criteria of randomized trials or high-quality observational studies.

Included Evidence

In **Braune 2018**, data from a German NeuroTransData multiple sclerosis registry was used to compare the effectiveness of dimethyl fumarate with fingolimod, teriflunomide, interferon beta, and glatiramer acetate in patients with relapsing-remitting multiple sclerosis using propensity score matching.[24] The study used data from registry patients that met the pre-defined criteria to match dimethyl fumarate with comparator populations baseline characteristics. The adjusted rate ratios for the time to first relapse were significantly lower for dimethyl fumarate compared to teriflunomide (0.53; 95% CI: 0.38-0.75), interferon beta (0.6, 95% CI: 0.44-0.79), and glatiramer acetate (0.65, 95% CI: 0.50-0.84). The annualized relapse rate was also in favor of dimethyl fumarate when compared to teriflunomide, interferon beta, and glatiramer acetate. There was no significant difference between dimethyl fumarate and fingolimod on these outcomes.

Rating of Included Evidence (Quality and Magnitude)

Braune 2018 is a well-performed observational study, however using GRADE criteria, evidence of this sort is considered low quality in the absence of specific criteria that would increase the quality

of evidence. Such criteria are not met in this case and so under the UPI Protocol we do not assess the magnitude of benefit in the absence of moderate or high-quality evidence.

Conclusion

After a careful review of the evidence, we conclude that Tecfidera (dimethyl fumarate) had a price increase *unsupported* by new clinical evidence.

3.9 Revlimid (Lenalidomide)

Introduction

Revlimid (lenalidomide, Celgene Corporation) is a thalidomide analogue that was first approved by the FDA in 2005.[25] Lenalidomide is indicated for the treatment of patients with myelodysplastic syndromes (associated with a deletion 5q abnormality with or without additional cytogenetic abnormalities), mantle cell lymphoma that has relapsed or progressed after two prior therapies, and multiple myeloma.[25] In multiple myeloma, lenalidomide is specifically indicated to be used in combination with dexamethasone, or as maintenance therapy following autologous hematopoietic stem cell transplantation.[25] Based on clinical input, only the multiple myeloma indication accounts for greater than 10% of use.

Price Increase

Over the 24-month (eight quarters) period for which price changes were assessed, lenalidomide's WAC price change was approximately 26%. Lenalidomide had total 2018 sales of approximately $6.4 billion. We received public comment that lenalidomide had experienced important price increases, but because of uncertainties in the volume of unit sales, we were unable to accurately determine the change in drug spending of lenalidomide due to price increases. Lenalidomide was included under the UPI Protocol allowance for reviewing up to three additional drugs.

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 lenalidomide as of January 2016. The manufacturer submitted 57 references (31 conference presentations and 26 published manuscripts) as new clinical information (published between January 1, 2016 and December 31, 2018) to be considered for our review. Of the 57 references, one study met our inclusion criteria of *new* information on benefits and/or harms within the indications stated above. The primary reasons for exclusion are provided in Table 3.9 (Appendix I provides more information on each study). We did not conduct an additional search for new clinical evidence.

Table 3.9. Reasons for Exclusion

Reasons for Exclusion	Number of References
Previously known information about lenalidomide (e.g., systematic review of randomized controlled trials published in 2016 or earlier)	12
Lenalidomide in all comparison arms (e.g., elotuzumab plus lenalidomide/dexamethasone vs. lenalidomide/dexamethasone)	20
Study design does not meet our criteria for assessing efficacy (e.g., single-arm study)	4
Intervention/comparison outside our scope (e.g., carfilzomib and dexamethasone vs. bortezomib and dexamethasone)	11
Outcomes not relevant to our scope (e.g., study does not present treatment specific results)	2
New evidence of no improvement in efficacy in the lenalidomide arm	1
Study population outside approved label indication	1
Abstract – limited information on study design	4
Study publication date outside scope timeline (2019)	1

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

Table 3.10. Summary of Clinical Evidence Identified

Baseline Evidence	Included Evidence
Evidence from two randomized controlled trials (McCarthy 2012 and Attal 2012) published in 2012 showed that lenalidomide maintenance after autologous stem-cell transplantation significantly prolonged progression-free and event-free survival among patients with multiple myeloma compared to placebo. Overall survival was not improved in the McCarthy 2012 and Attal 2012 trials after a median follow-up of 30 and 34 months, respectively.[26,27]	**Holstein 2017:** Longer-term follow-up data from one randomized controlled trial showed that lenalidomide maintenance therapy following autologous stem cell transplant significantly improves time-to-progression and overall survival compared to placebo.[28]

Included Evidence

Holstein 2017 evaluated the efficacy and safety of lenalidomide versus placebo following autologous stem cell transplant in newly diagnosed myeloma patients at 91-months median follow-up.[28] Patients were randomized 1:1 to either lenalidomide (n=231) or placebo (n=229). At the follow-up time of 91 months, the median time to disease progression for lenalidomide versus placebo was 57.3 months versus 28.9 months (HR=0.57; 95% CI, 0.46-0.71; p<0.0001), and median overall survival was 113.8 months with lenalidomide versus 84.1 months with placebo (HR=0.61; 95% CI, 0.46-0.80; p=0.0004). Lenalidomide was observed to be superior to placebo regardless of whether patients were in a complete response at the time of randomization or whether they had received thalidomide or lenalidomide induction therapy. Consistent with what was previously

known, there were more hematological adverse events and second primary malignancies in the lenalidomide group compared to the placebo group.

Rating of Included Evidence (Quality and Magnitude)

Prior to Holstein 2017, a 2012 analysis of the same trial (McCarthy 2012) showed a hazard ratio for overall survival of 0.52 (95% CI: 0.26-1.02) after a median follow-up of 34 months. A second randomized controlled trial, Attal 2012, at a median follow-up of 30 months showed improvements in progression-free survival and event-free survival, but there was no benefit on overall survival (hazard ratio 1.25; p=0.29). The second randomized controlled trial also reported overall survival at 45 months median follow-up and there continued to be no benefit (hazard ratio 1.06; p=0.70). Thus, uncertainty remained as to whether lenalidomide improved overall survival. With downrating for inconsistency, Holstein 2017 provided moderate quality evidence of an additional net benefit (overall survival improvement of 30 months) that is clearly substantial if real.

Conclusion

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

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APPENDICES

Appendix A. Humira

Table A1. Reasons for Exclusion

Citation	Reasons for Exclusion
Khraishi M, Bessette L, Chow A, et al. Canadian adalimumab post-marketing observational epidemiological study assessing the effectiveness of adalimumab vs non-biologic dmards in psoriatic arthritis (COMPLETE-PSA): 12-month effectiveness data. Ann Rheum Dis. 2018 June; 77 (S2): 1592.	Abstract – limited information on study design
Kirby B, Maa JF, Festini T, et al. Sustained response to adalimumab over multiple years in patients with plaque psoriasis: analyses from the British Association of Dermatologists Biologic Interventions Register (BADBIR). Br J Dermatol. 2017 Nov 1; 177 (5): E262-E263.	Abstract – limited information on study design
Strand V, Husni ME, Betts K, et al. Network Meta-Analysis of Tumor Necrosis Factor, Interleukin, and Phosphodiesterase-4 Inhibitors in the Treatment of Psoriatic Arthritis. Presented at the 74th Annual Meeting of the American Academy of Dermatology. 2016 March; Washington DC.	Abstract – limited information on study design
Strand V, Husni ME, Griffith J, et al. Network Meta-Analysis of Targeted Immunomodulators in the Treatment of Psoriatic Arthritis Patients without Prior Biologic Treatment. Arthritis Rheum. 2018 Sep; 70: 701.	Abstract – limited information on study design
Hyams JS, Dubinsky M, Rosh J, 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. Aliment Pharmacol Ther. 2019 Jan;49(2):155-164.	Adalimumab in all comparison arms
Burmester GR, Kaeley GS, Kavanaugh AF, et al. Treatment efficacy and methotrexate-related toxicity in patients with rheumatoid arthritis receiving methotrexate in combination with adalimumab. RMD Open. 2017 Sep 17;3(2):e000465.	Adalimumab in all comparison arms
Kaeley GS, Evangelisto AM, Nishio MJ, et al. Methotrexate Dosage Reduction Upon Adalimumab Initiation: Clinical and Ultrasonographic Outcomes from the Randomized Noninferiority MUSICA Trial. J Rheumatol. 2016 Aug;43(8):1480-9.	Adalimumab in all comparison arms
Kaeley GS, MacCarter DK, Goyal JR, et al. Similar Improvements in Patient-Reported Outcomes Among Rheumatoid Arthritis Patients Treated with Two Different Doses of Methotrexate in Combination with Adalimumab: Results From the MUSICA Trial. Rheumatol Ther. 2018 Jun;5(1):123-134.	Adalimumab in all comparison arms
Pappas D, Griffith J, Schlacher CA, et al. Effectiveness of adalimumab combination therapy with methotrexate and non-methotrexate csdmards: results from the corrona rheumatoid arthritis registry. Ann Rheum Dis. 2017 June; 76 (S2): 552-553.	Adalimumab in all comparison arms
Smolen J, Mostafa N, Huang X, et al. The value of adalimumab trough levels and clinical assessments in predicting clinical response in patients with established rheumatoid arthritis and an inadequate response to methotrexate. Ann Rheum Dis. 2018 June; 77 (S2): 311.	Adalimumab in all comparison arms

Augustin M, Calimlim B, Williams D, et al. Adalimumab improves health-related quality of life in patients with fingernail psoriasis. J Am Acad Dermatol. 2017 Jun; 76 (6): AB33	Indication accounts for less than 10% of use
Elewski BE, Rich PA, Behrens F, et al. Primary efficacy and safety of adalimumab in nail psoriasis from the first 26 weeks of a phase-3, randomized, placebo-controlled trial with subanalysis in patients with and without psoriatic arthritis. Ann Rheum Dis. 2017 June; 76 (S2): 1319-1320.	Indication accounts for less than 10% of use
Aletaha D, Panaccione R, Davis M, Johnson S, Skup M, Garg V. OP0076 Risk of developing additional immune mediated manifestations for patients with systemic arthritides. Ann Rheum Dis. 2017 June; 76 (S2): 83.	Intervention/comparison outside our scope
Armstrong AW, Duffin KC, Geng Z, et al. Bridging the Gap Between Clinical Trials and Real-World Practice: Predicting Psoriasis Area Severity Index Scores (PASI) Based on Body Surface Area (BSA) and Physicians Global Assessment (PGA). Presented at the 77th Annual Meeting of the American Academy of Dermatology. 2019 March; Washington DC.	Intervention/comparison outside our scope
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Boehncke WH, Horvath R, Dalkilio E, et al. Clinical Specialty Setting As a Determinant for Disease Management in Patients with Psoriatic Arthritis: An Interim Analysis of the Cross-Sectional Observational Study. Arthritis Rheum. 2017 Oct; 69: 2530.	Intervention/comparison outside our scope
Boehncke WH, Piercy J, Chen S, et al. Impact of Patient Perception of Psoriasis and Psoriatic Arthritis Severity on Patient-Reported Outcomes: An Analysis from The Adelphi Database. Ann Rheum Dis. 2016 June; 75 (S2): AB0749.	Intervention/comparison outside our scope
Bossuyt P, D'Haens G, Panaccione R, et al. De-escalating therapy in patients with Crohn's disease receiving adalimumab: subgroup analysis of the calm study FREE. Gut. 2019; 68 (S2): A70-A71.	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. J Manag Care Spec Pharm. 2019 Jul;25(7):770-779.	Intervention/comparison outside our scope
Chang C, Chen K, Chen Y, et al. Prediction of Flaring in Rheumatoid Arthritis Patients upon Biologics Dose Tapering: A Chart Review Study in Taiwan. Ann Rheum Dis. 2016 June; 75 (S2): THU0161.	Intervention/comparison outside our scope
Colombel JF, Panaccione R, Bossuyt P, et al. A Treat to Target Approach Decreases the Rate of CD-Related Adverse Outcomes versus a Clinical Approach in Patients With Moderate to Severely Active Crohn's Disease: Data From CALM. Am J Gastroenterol. 2017 Oct; 112: S321.	Intervention/comparison outside our scope
Colombel JF, Panaccione R, Bossuyt P, et al. Superior endoscopic and deep remission outcomes in adults with moderate to severe Crohn's disease managed with treat to target approach versus clinical symptoms: data from CALM. Gastroenterology. 2017 Apr 1;152(5):S155.	Intervention/comparison outside our scope

Cross RK, Osterman MT, Panaccione R, et al. The Incidence of Cardiovascular Events in Patients with Crohn's Disease Treated with Vedolizumab and Anti-TNF Therapies. Gastroenterology. 2017 Apr 1;152(5):S577-8.	Intervention/comparison outside our scope
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Dubinsky M, Cross Jr R, Sandborn W, et al. The Incidence of Extraintestinal Manifestations in Patients with Inflammatory Bowel Disease Treated with Vedolizumab and Anti-TNF Therapies. Inflamm Bowel Dis. 2017 Feb ;23(S1):S17-8.	Intervention/comparison outside our scope
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Ghosh S, Casellas F, O'shea C, et al. Extraintestinal Manifestations and Quality of Life in Patients with Ulcerative Colitis: 1-Year Data from Iconic. Gastroenterology. 2019 May 1;156(6):S867.	Intervention/comparison outside our scope
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Hernandez J, Maciel G, Chaves L, et al. Impact of Abbvie's patient support program (PSP) on persistence with adalimumab therapy among patients with rheumatoid arthritis in Uruguay. Value Health. 2017 May; 20 (5): A148.	Intervention/comparison outside our scope
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Mease P, Mittal M, Skup M, et al. Impact of a Patient Support Program on Abandonment of Adalimumab Treatment Initiation in Patients with Rheumatoid Arthritis, Ankylosing Spondylitis, and Psoriatic Arthritis. Arthritis Rheum. 2016 October; 68: 80.	Intervention/comparison outside our scope
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Pappas DA, Griffith J, Litman HJ, et al. Time to Initiation of Biologic Agents Is Associated with Glucocorticoid Use: Results from the Corrona Registry. Arthritis Rheum. 2016 Oct; 68: 2597.	Intervention/comparison outside our scope
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van den Bosch F, Ostor A, Wassenberg S, et al. Impact of Participation in the Adalimumab (Humira) Patient Support Program on Patient Reported Outcomes Among Patients with Rheumatoid Arthritis: Passion Study. Arthritis Rheum. 2016 Oct; 68: 1480.	Intervention/comparison outside our scope
Van den Bosch F, Ostor AJK, Wassenberg S, et al. Impact of Participation in the Adalimumab (Humira) Patient Support Program on Rheumatoid Arthritis Treatment Course: Results from the PASSION Study. Rheumatol Ther. 2017 Jun;4(1):85-96.	Intervention/comparison outside our scope
Van Den Bosch F, Wassenberg S, Haraoui B, et al. The Impact of Participation in an Adalimumab (Humira) Patient Support Program on the Onset and Management of Disease Flares. Arthritis Rheum. 2018 Sep; 70: 1192.	Intervention/comparison outside our scope
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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. Ann Rheum Dis. 2018 June; 77 (S2): 602.	Intervention/comparison outside our scope
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Aletaha D, Li Y, Hojnik M, Ganz F. Impact of Methotrexate Dose on Adalimumab Efficacy in Psoriatic Arthritis: A Subanalysis of ADEPT. Clin Exp Rheumatol. 2016 Jul; 34 (4): 785.	Study design does not meet our criteria for assessing efficacy
Aletaha D, Snedecor SJ, Ektare V, et al. Clinical and economic analysis of outcomes of dose tapering or withdrawal of tumor necrosis factor-α inhibitors upon achieving stable disease activity in rheumatoid arthritis patients. Clinicoecon Outcomes Res. 2017 Jul 28;9:451-458.	Outcomes not relevant to our scope
Armstrong A, Betts K, Sundaram M, Li J, Wu E. Relative efficacy and costs per responder for adalimumab versus secukinumab in the treatment of moderate to severe psoriasis. J Am Acad Dermatol. 2016 May 1;74(5): AB267.	Study design does not meet our criteria for assessing efficacy
Armstrong A, Merola J, Yang M, et al. Drug cost per responder for the treatment of moderate-to-severe psoriasis and active psoriatic arthritis. J Am Acad Dermatol. 2017 Jun; 76 (6): AB105.	Outcomes not relevant to our scope
Armstrong AW, Betts KA, Signorovitch JE, et al. Number needed to treat and costs per responder among biologic treatments for moderate-to-severe psoriasis: a network meta-analysis. Curr Med Res Opin. 2018 Jul;34(7):1325-1333.	Outcomes not relevant to our scope
Bergman MJ, Zueger P, Song J, et al. Inflammatory bowel disease is associated with a substantial economic burden in patients with psoriatic arthritis and in patients with ankylosing spondylitis. Arthritis Rheum. 2018 Sep; 70: 285.	Outcomes not relevant to our scope
Chiorean M, Afzali A, Cross R, et al. Economic Impact of Switching from Anti-TNF Therapy to Adalimumab, Infiximab or other Anti-TNF Compared with Switching from Anti-TNF Therapy to Vedolizumab. Inflamm Bowel Dis. 2018 Jan; 24(S1):S51-2.	Outcomes not relevant to our scope
Emery P, Smolen JS, Ganguli A, et al. Effect of adalimumab on the work-related outcomes scores in patients with early rheumatoid arthritis receiving methotrexate. Rheumatology (Oxford). 2016 Aug;55(8):1458-65.	Study design does not meet our criteria for assessing efficacy
Gibofsky A, Garg V, Yang M, et al. Estimating the short-term costs associated with non-medical switching in rheumatic diseases. Ann Rheum Dis. 2018 June; 77 (S2): 1372.	Outcomes not relevant to our scope
Kennedy NA, Heap GA, Green HD, et al; UK Inflammatory Bowel Disease Pharmacogenetics Study Group. Predictors of anti-TNF treatment failure in anti-TNF-naive patients with active luminal Crohn's disease: a prospective, multicentre, cohort study. Lancet Gastroenterol Hepatol. 2019 May;4(5):341-353.	Outcomes not relevant to our scope
Langley RG, Li J, Betts KA, et al. Cost-Effectiveness of Adalimumab and Secukinumab as First-Line Treatments of Moderate-to-Severe Psoriasis and Active Psoriatic Arthritis. Presented at 25th European Academy of Dermatology and Venereology Congress (EADV). 2016 September- October; Vienna, Austria.	Outcomes not relevant to our scope
Li J, Betts KA, Xiang CQ, et al. Cost per Responder Analysis of Treatments for Moderate-to-Severe Psoriasis in the United Kingdom. Presented at 25th European Academy of Dermatology and Venereology Congress (EADV). 2016 September- October; Vienna, Austria.	Outcomes not relevant to our scope

Liu Y, Garg V, Yang M, et al. Economic impact of non-medical switching from originator biologics to biosimilars–a systematic literature review. Ann Rheum Dis. 2018 June; 77 (S2): 1731-1732.	Intervention/comparison outside our scope
Liu Y, Skup M, Lin J, Chao J. Impact of nonmedical switching on health care costs: A claims database analysis. J Am Acad Dermatol. 2016 May 1;74(5): AB118.	Outcomes not relevant to our scope
Panaccione R, Colombel JF, Bossuyt P, et al. Long-term cost-effectiveness of tight control for Crohn's disease with adalimumab-based treatment: economic evaluation beyond 48 weeks of CALM trial. J Crohns Colitis. 2018 Jan 16;12(S1):S074-5.	Outcomes not relevant to our scope
Papp K, Yang H, Zhou Z, et al. Dose-Escalation Versus Switching: Healthcare Resource Utilisation and Costs of Adalimumab-Treated Adults With Psoriasis. Presented at 25th European Academy of Dermatology and Venereology Congress (EADV). 2017 September; Geneva, Switzerland.	Outcomes not relevant to our scope
Papp K, Yang H, Zhou Z, et al. Healthcare resource use and costs of adalimumab-treated adults with psoriasis who dose escalated versus switched to another biologic agent. Presented at 25th European Academy of Dermatology and Venereology Congress (EADV). 2016 September- October; Vienna, Austria.	Outcomes not relevant to our scope
Reinisch W, Panaccione R, Bossuyt P, et al. Factors Driving Treatment Escalation in Crohn's Disease in the Calm Trial. Gastroenterology. 2018 May 1;154(6):S-81.	Study design does not meet our criteria for assessing efficacy
Sandborn W, Sakuraba A, Wang A, et al. Comparison of real-world outcomes of adalimumab and infliximab for patients with ulcerative colitis in the United States. Congress of ECCO – European Crohn's and Colitis Organisation. 2017; 11 (S1): S426.	Outcomes not relevant to our scope
Smolen JS, Emery P, Zhang H, et al. Predicting maintenance of response based on disease characteristics and early clinical response in rheumatoid arthritis patients upon withdrawal of adalimumab. Ann Rheum Dis. 2017 June; 76 (S2): 785.	Outcomes not relevant to our scope
Smolen JS, Gladman D, McNeil HP, et al. Predicting adherence to therapy in rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis: a large cross-sectional study. RMD Open. 2019 Jan 11;5(1):e000585.	Outcomes not relevant to our scope
Smolen JS, Sunkureddi P, Anderson JK, et al. The Ability of Patients with Early Rheumatoid Arthritis to Taper Low-Dose Glucocorticoids on Methotrexate Monotherapy and in Combination with Adalimumab. Arthritis Rheum. 2017 Oct; 69: 1420.	Outcomes not relevant to our scope
Smolen JS, Wang X, Sainsbury I, Kavanaugh A. Predicting DAS28-CRP< 2.6 And Low Disease Activity Status at 6 Months Based on Early Clinical Response in Rheumatoid Arthritis Patients. Ann Rheum Dis. 2016 June; 75 (S2): THU0029	Outcomes not relevant to our scope
Strand V, Alto P, Husni E, et al. Network metaanalysis and cost per responder of tumor necrosis factor, interleukin, and phosphodiesterase inhibitors in the treatment of psoriatic arthritis. J Am Acad Dermatol. 2016 May; 74 (5S): AB260.	Abstract – limited information on study design

Strand V, Tundia N, Song Y, Macaulay D, Fuldeore M. Economic Burden of Non-Responders to Biologic DMARD Treatments in Rheumatoid Arthritis. Arthritis Rheum. 2016 Oct; 68: 2617.	Outcomes not relevant to our scope
Tillett W, Piercy J, Chen S, Ganz F. Impact of Disease Flare Perception on Work Productivity and Treatment Satisfaction in Patients with Psoriatic Arthritis in Real World Setting. Arthritis Rheum. 2016 Oct; 68: 2730.	Intervention/comparison outside our scope
Travis S, Feagan BG, Peyrin-Biroulet L, et al. The Costs of Care for Patients With Ulcerative Colitis: Effect of Adalimumab on Health Care Resources Utilisation in Clinical Practice From INSPIRADA. Gastroenterology. 2016 Apr 1;150(4):S631.	Outcomes not relevant to our scope
Wu J, Sundaram M, Gauthier G, Guérin A, Thompson-Leduc P. Comparison of outcomes between psoriasis (Ps) patients (Pts) who switched from etanercept (ETA) to adalimumab (ADA) versus to ustekinumab (UST): 2524. J Am Acad Dermatol. 2016 May 1;74(5): AB241	Outcomes not relevant to our scope
Wu JJ, Bereswill M, Camez A, Valdecantos WC. Baseline characteristics associated with drug survival in the ESPRIT 10-year postmarketing surveillance registry of adalimumab for moderate to severe psoriasis. J Am Acad Dermatol. 2017 Jun; 76 (6): AB54.	Outcomes not relevant to our scope
Wu JJ, Guérin A, Gauthier G, Sundaram M. Healthcare resource utilization, healthcare costs and dose escalation in psoriasis patients initiated on ustekinumab versus adalimumab: a retrospective claim study. J Dermatolog Treat. 2017 Jun;28(4):290-298.	Outcomes not relevant to our scope
Yang M, Galebach PJ, Signorovitch JE, Garg V. Effectiveness and healthcare costs among stabilised rheumatoid arthritis patients with dose reduction of adalimumab or etanercept in real world. Clin Exp Rheumatol. 2017 Sep-Oct;35(5):791-798.	Outcomes not relevant to our scope
Zhou ZY, Griffith J, Du EX, et al. Economic Burden of Switching to a Non-Tumor Necrosis Factor Inhibitor Versus a Tumor Necrosis Factor Inhibitor Biologic Therapy among Patients with Rheumatoid Arthritis. Adv Ther. 2016 May;33(5):807-23.	Outcomes not relevant to our scope
Crowley J, Gisondi P, Geng Z, Servin O. Long-term safety and efficacy of adalimumab from the phase 3 randomized placebo-controlled trial in patients with nail and skin psoriasis. J Am Acad Dermatol. 2018 Sep 1;79(3): AB181.	Previously known information about adalimumab related to efficacy
Hanauer S, Sandborn WJ, Colombel JF, et al. Rapid Changes in Laboratory Parameters and Early Response to Adalimumab: A Pooled Analysis From Patients With Ulcerative Colitis in 2 Clinical Trials. J Crohns Colitis. 2019 Feb 6. doi: 10.1093/ecco-jcc/jjz031. [Epub ahead of print]	Previously known information about adalimumab related to efficacy
Murray E, Butylkova Y, Ellis A, et al. A Systematic Review and Meta-Analysis of Comparative Efficacy of Biologics in Treating Patients with Rheumatoid Arthritis: Assessment of Long-Term Radiographic Progression from Published Clinical Trials. Arthritis Rheum. 2016 Oct; 68: 610.	Previously known information about adalimumab related to efficacy
Sandborn WJ, Sakuraba A, Wang A, et al. Comparison of real-world outcomes of adalimumab and infliximab for patients with ulcerative colitis in the United States. Curr Med Res Opin. 2016 Jul;32(7):1233-41.	Previously known information about adalimumab related to efficacy

Suzuki Y, Motoya S, Hanai H, et al. Four-year maintenance treatment with adalimumab in Japanese patients with moderately to severely active ulcerative colitis. J Gastroenterol. 2017 Sep;52(9):1031-1040.	Previously known information about adalimumab related to efficacy
Armstrong A, Lambert J, Prussick R, et al. Efficacy of adalimumab compared with placebo stratified by baseline disease severity in patients with moderate to severe psoriasis from the CHAMPION and REVEAL studies. J Am Acad Dermatol. 2018 Sep 1;79(3): AB123.	Previously known information about adalimumab related to safety
Bewley A, Maa JF, Servin OR, et al. Metabolic Parameters of Patients With Plaque Psoriasis Receiving Adalimumab Over Multiple Years: Analyses From the British Association of Dermatologists' Biological Interventions Register. Presented at 27th European Academy of Dermatology and Venereology Congress (EADV). 2018 September; Paris, France.	Previously known information about adalimumab related to safety
Bossuyt P, Atreya R, Taxonera C, et al. Long-term safety of adalimumab in patients with moderate-to-severe ulcerative colitis: Interim results of a non-interventional registry, LEGACY. J Crohns Colitis. 2018 Jan; 12(S1): S032.	Previously known information about adalimumab related to safety
Burmester GR, Landewé R, Genovese MC, et al. Adalimumab long-term safety: infections, vaccination response and pregnancy outcomes in patients with rheumatoid arthritis. Ann Rheum Dis. 2017 Feb;76(2):414-417.	Previously known information about adalimumab related to safety
Colombel JF, D'Haens G, Reinisch W, et al. PYRAMID Registry: Long-term Safety of Adalimumab by Age in Patients With Crohn's Disease: 717. Am J Gastroenterol. 2017 Oct 1;112:S396-7.	Previously known information about adalimumab related to safety
Curtis JR, Elewaut D, Chen S, et al. Incidence of Inflammatory Bowel Disease Events in Adalimumab (HUMIRA) Clinical Trials Across Indications. Arthritis Rheum. 2016 Oct; 68: 700.	Previously known information about adalimumab related to safety
Curtis JR, Elewaut D, Chen S, et al. Incidence of inflammatory bowel disease events in adalimumab clinical trials across indications. Ann Rheum Dis. 2017 June; 76 (S2): 654-655.	Previously known information about adalimumab related to safety
D'Haens G, Reinisch W, Satsangi J, et al. Long-term safety of adalimumab in patients with Crohn's disease: final data from PYRAMID registry. J Crohns Colitis. 2017 Jan 26;11(S1):S256-7.	Previously known information about adalimumab related to safety
Harrold LR, Griffith J, Litman HJ, et al. Long-Term, Real-World Safety of Adalimumab in Rheumatoid Arthritis. Arthritis Rheum. 2018; 70: 1529.	Previously known information about adalimumab related to safety
Kerdel F, Menter A, Wu JJ, et al. Seven-year interim results from the ESPRIT 10-year postmarketing surveillance registry of adalimumab for moderate to severe psoriasis. J Am Acad Dermatol. 2017 Jun; 76 (6): AB234.	Previously known information about adalimumab related to safety

Kirby B, Maa JF, Festini T, Calimlim B, Servin OR. Sustained response to adalimumab over multiple years in patients with plaque psoriasis: analyses from the British Association of Dermatologists Biologic Interventions Register (BADBIR). Brit J Derm. 2017 Nov; 177 (5): E262-E263.	Previously known information about adalimumab related to safety
Menter A, Thaçi D, Wu JJ, et al. Long-Term Safety and Effectiveness of Adalimumab for Moderate to Severe Psoriasis: Results from 7-Year Interim Analysis of the ESPRIT Registry. Dermatol Ther (Heidelb). 2017 Sep;7(3):365-381.	Previously known information about adalimumab related to safety
Prussick R, Maa JF, Servin OR. Effect of adalimumab treatment on metabolic parameters over 3 years: Integrated analysis from phase 2/3 clinical trials in patients with moderate to severe psoriasis. J Am Acad Dermatol. 2017 Jun; 76 (6): AB108.	Previously known information about adalimumab related to safety
Strober B, Crowley J, Langley R, et al. Real-World Evidence of Adalimumab Safety in Psoriasis Registries. Presented at 26th European Academy of Dermatology and Venereology Congress (EADV). 2017 September; Geneva, Switzerland.	Previously known information about adalimumab related to safety
Strober B, Crowley J, Langley RG, et al. Systematic review of the real-world evidence of adalimumab safety in psoriasis registries. J Eur Acad Dermatol Venereol. 2018 Dec;32(12):2126-2133.	Previously known information about adalimumab related to safety
Thaçi D, Menter A, Wu J, et al. An 8-year interim safety analysis by geographic region of the ESPRIT 10-year postmarketing surveillance registry of adalimumab for moderate to severe psoriasis. J Am Acad Dermatol. 2018 Sep 1;79(3): AB36.	Previously known information about adalimumab related to safety
Thaci D, Menter A, Wu JJ, et al. Long-Term Safety and Effectiveness of Adalimumab for Moderat-to-Severe Psoriasis: Results from the Eight-Year Interim Analysis of the ESPIRIT Registry. SKIN The Journal of Cutaneous Medicine. 2017 Oct 27;1(3.1):s22.	Previously known information about adalimumab related to safety
Thaci D, Wu JJ, Abramovits W, et al. Long-term Real-World Safety and Effectiveness of Adalimumab for Moderate to Severe Psoriasis: Results from the Nine-Year Interim Analysis of the ESPRIT Registry. Presented at 27th European Academy of Dermatology and Venereology Congress (EADV). 2018 September; Paris, France.	Previously known information about adalimumab related to safety
Turner D, Koletzko S, Winter H, et al. Safety of adalimumab in children and adolescents with moderate-to-severe Crohn's disease: interim results of the CAPE registry. Journal of Crohn's and Colitis. 2018 Jan 16;12(S1):S035.	Previously known information about adalimumab related to safety
Wu JJ, Abramovits W, Kerdel F, et al. Eight-Year Interim Results from the ESPRIT 10-Year Postmarketing Surveillance Registry of Adalimumab for Moderate to Severe Psoriasis. Acta Derm Venereol. 2018 Jan; 98: 25-26.	Previously known information about adalimumab related to safety

Wu JJ, Abramovits W, Kerdel F, et al. Treatment Emergent Cardiovascular Events, Serious Infections, and Malignancies from the ESPRIT 10-Year Postmarketing Surveillance Registry of Adalimumab for Moderate to Severe Psoriasis: An 8-Year Interim Safety Analysis. Presented at 26th European Academy of Dermatology and Venereology Congress (EADV). 2017 September; Geneva, Switzerland.	Previously known information about adalimumab related to safety
Wu JJ, Abramovits W, Valdecantos WC, et al. ESPRIT Registry Nine-Year Interim Real-World Safety, Effectiveness, and Patient-Reported Outcomes of Adalimumab for Moderate to Severe Psoriasis. Presented at the American Academy of Dermatology Annual Meeting. 2019 March; Washington DC.	Previously known information about adalimumab related to safety
Wu JJ, Singh R, Yang M, et al. Long-Term Safety Profile of Adalimumab versus Ustekinumab in Psoriasis - A Real World Matching-Adjusted Indirect Comparison (MAIC). Presented at the American Academy of Dermatology Annual Meeting. 2019 March; Washington DC.	Previously known information about adalimumab related to safety
Breedveld F, Wang X, Cardoso A, et al. The Relative Performance of 28-Joint Disease Activity Score Based on C-Reactive Protein with Three Versus Four Components in Patients with Rheumatoid Arthritis. Arthritis Rheum. 2016 Oct; 68: 495.	Study design does not meet our criteria for assessing efficacy
Declerck P, Tebbey PW. Importance of manufacturing consistency of the glycosylated monoclonal antibody adalimumab (Humira [R]) and potential impact on the clinical use of biosimilars. GaBI J. 2016 Jun 1;5(2):70-4.	Study design does not meet our criteria for assessing efficacy
Emery P, Burmester G, Naredo E, et al. Low inflammation on magnetic resonance imaging in patients with rheumatoid arthritis that achieved sustained clinical remission on adalimumab: data from the predictra study. Ann Rheum Dis. 2018 June; 77 (S2): 283-284.	Study design does not meet our criteria for assessing efficacy
Ghosh S, Casellas F, O'shea C, et al. Disease-Related Worries and Concerns in Patients with Ulcerative Colitis: 1-Year Data from Iconic. Gastroenterology. 2019 May;156(6):S438.	Study design does not meet our criteria for assessing efficacy
Ghosh S, Peyrin-Biroulet L, Casellas F, et al. Healthcare Resource Utilization and Quality of Life in Patients With Ulcerative Colitis by Disease Severity: Baseline Data From ICONIC. Presented at 25th United European Gastroenterology Week. 2017 October-November; Barcelona, Spain.	Study design does not meet our criteria for assessing efficacy
Husni ME, Griffith J, Betts K, et al. Thresholds of Benefit-Risk Trade-Offs from the Patient Perspective for Treatment Decisions in Moderate-to-Severe Rheumatoid Arthritis. Arthritis Rheum. 2016 Oct; 68: 2505.	Study design does not meet our criteria for assessing efficacy
Kavanaugh A, Griffith J, Karki C, et al. Disease Activity and Biologic Use in Patients with Rheumatoid Arthritis and Psoriatic Arthritis in The Past 10 Years: Results from The Corrona Registry. Ann Rheum Dis. 2016 June; 75 (S2): THU0604.	Study design does not meet our criteria for assessing efficacy
Keystone EC, Betts KA, Schlacher CA, et al. Incremental Benefit of Radiographic Inhibition on Long-Term Outcomes in Patients with Rheumatoid Arthritis. Arthritis Rheum. 2016 Oct; 68: 2621.	Study design does not meet our criteria for assessing efficacy
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. Rheumatology (Oxford). 2019 Jun 1;58(6):1025-1033.	Study design does not meet our criteria for assessing efficacy

Leonardi C, Papp K, Strober B, et al. Comprehensive long-term safety of adalimumab from 18 clinical trials in adult patients with moderate-to-severe plaque psoriasis. Br J Dermatol. 2019 Jan;180(1):76-85.	Study design does not meet our criteria for assessing efficacy
Maaser C, Petersen F, Helwig U, et al. Monitoring Response to Anti-TNF Therapy in Ulcerative Colitis Patients by Gastrointestinal Ultrasound: Subanalysis from Trust&UC. Gastroenterology. 2019 May;156(6):S612.	Study design does not meet our criteria for assessing efficacy
Mease PJ, Chen S, Ganz F, Tillett W. Correlation of the routine assessment of patient index data (RAPID-3) with other psoriatic arthritis composite disease activity measures in patients receiving adalimumab. Ann Rheum Dis. 2017 June; 76 (S2): 682-683.	Study design does not meet our criteria for assessing efficacy
Panaccione R, Rutgeerts P, Sandborn WJ, et al. Adalimumab Efficacy and Safety by Disease Duration: Analysis of Pooled Studies of Crohn's Disease. Gastroenterology. 2017 Apr 1;152(5):S744.	Study design does not meet our criteria for assessing efficacy
Pappas DA, Karki C, Litman HJ, et al. Impact of Adalimumab on Prednisone Use in Patients with Rheumatoid Arthritis in a Real World Setting-Results from the Corrona Registry. Arthritis Rheum. 2017 October; 69: 1422.	Study design does not meet our criteria for assessing efficacy
Sandborn WJ, Lewis J, Panes J, et al. Association Between Proposed Definitions of Clinical Remission/Response and Well-Being in Patients with Crohn's Disease. United Eur Gastroent. 2018 October; 8 (S): A641.	Study design does not meet our criteria for assessing efficacy
Scoville C, Suboticki J, Zhong S, Keystone E. The relevance of elevated crp as an inclusion criterion in clinical trials in patients with rheumatoid arthritis. Ann Rheum Dis. 2017 June; 76 (S2): 230-231.	Study design does not meet our criteria for assessing efficacy
Scoville C, Suboticki J, Zhong S, Keystone E. The Relevance of Elevated CRP As an Inclusion Criterion in Clinical Trials in Patients with Rheumatoid Arthritis. Arthritis Rheum. 2017 Sep; 69: 1352.	Study design does not meet our criteria for assessing efficacy
Smolen J, Aletaha D, Gladman DD, et al. Outcomes associated with achievement of various treatment targets in patients with psoriatic arthritis receiving adalimumab. Ann Rheum Dis. 2017 June; 77 (S2): 677.	Study design does not meet our criteria for assessing efficacy
Smolen J, Gabay C, Aletaha D, et al. The importance of sustained remission for longterm outcomes in patients with rheumatoid arthritis. Ann Rheum Dis. 2017 June; 76 (S2): 242.	Study design does not meet our criteria for assessing efficacy
Smolen JS, Gladman DD, McNeil HP, et al. Treatment Adherence and Attitudes towards Systemic Medications in Patients with Rheumatoid Arthritis in Different Geographical Regions. Ann Rheum Dis. 2016 June; 75 (S2): THU0616	Study design does not meet our criteria for assessing efficacy
Baker C, Lambert J, Geng Z, Servin OR. Efficacy and Safety of Adalimumab in Patients with Moderate-to-Severe Nail Psoriasis by Level of Psoriasis-Affected Body Surface Area. Presented at 26th European Academy of Dermatology and Venereology Congress (EADV). 2017 September; Geneva, Switzerland.	Study design does not meet our criteria for assessing efficacy
Betts KA, Griffith J, Friedman A, et al. An indirect comparison and cost per responder analysis of adalimumab, methotrexate and apremilast in the treatment of methotrexate-naïve patients with psoriatic arthritis. Curr Med Res Opin. 2016;32(4):721-9.	Study design does not meet our criteria for assessing efficacy

Burmester GR, Panaccione R, Gordon KB, et al. Long-Term Safety of Adalimumab (HUMIRA) in Adult Patients from Global Clinical Trials across Multiple Indications: An Updated Analysis in 29,987 Patients Representing 56,951 Patient-Years. Arthritis Rheum. 2017 Sep; 70: 2481.	Study design does not meet our criteria for assessing efficacy
Chiorean M, Afzali A, Zhou Z, et al. Patient Outcomes and Economic Impacts of Switching From Anti -TNF to Anti -TNF Therapy Compared With Switching From Anti -TNF Therapy to Vedolizumab. Presented at Digestive Disease Week. 2017 May; Chicago, Illinois.	Study design does not meet our criteria for assessing efficacy
Coates LC, Mease PJ, Chen K, et al. Long-Term Inhibition of Radiographic Progression with Originator Adalimumab in Patients with Moderate to Severe Psoriatic Arthritis with or without Radiographic Damage at Baseline. Arthritis Rheum. 2018 Sep; 70: 2606.	Study design does not meet our criteria for assessing efficacy
Elewski B, Crowley J, Geng Z, Servin OR. Outcomes of Adalimumab Treatment in Patients with Moderate-to-Severe Nail Psoriasis by Previous Methotrexate or Biologics Treatment: From a Phase-3, Placebo-Controlled Trial. Presented at 26th European Academy of Dermatology and Venereology Congress (EADV). 2017 September; Geneva, Switzerland.	Study design does not meet our criteria for assessing efficacy
Feldman SR, Kane SV, Collins RM, et al. Hesitancy toward adalimumab therapy decreases in psoriasis and psoriatic arthritis patients enrolled in a nurse care management program. J Am Acad Dermatol. 2017 Jun; 76 (6): AB152.	Study design does not meet our criteria for assessing efficacy
Gniadecki R, Leonardi CL, Gordon KB, et al. Long-term optimization of outcomes with flexible adalimumab dosing in patients with moderate to severe plaque psoriasis. J Eur Acad Dermatol Venereol. 2018 Aug;32(8):1297-1304.	Study design does not meet our criteria for assessing efficacy
Gottlieb AB, Elewski BE, Okun MM, et al. Adalimumab for Nail Psoriasis: Efficacy and Safety from the Open-Label Extension of a Phase-3, Randomized, Placebo-Controlled Trial. SKIN The Journal of Cutaneous Medicine. 2017 Oct 27;1(3.1):s97.	Study design does not meet our criteria for assessing efficacy
Grant A, Otley A, Escher J, et al. Assessment of IMPACT III emotional and social functioning domain scores in adalimumab-treated paediatric patients with Crohn's disease. J Crohns Colitis. 2016 Mar; 10: S424-S425.	Study design does not meet our criteria for assessing efficacy
Harvey BP, Cohen-Solal J, Kaymakcalan Z. Adalimumab: tnf complexes are cleared more efficiently by human osteoclasts than those with etanercept through fcg-receptor binding and internalisation. Ann Rheum Dis. 2018 June; 77 (S2): 893.	Study design does not meet our criteria for assessing efficacy
Hyams JS, Ruemmele F, Rosh J, et al. Contribution of Individual PCDAI Subscores to Remission in Pediatric Patients with Crohn's Disease: Results from IMAgINE 1 Trial. Presented at the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition 28th Annual Meeting. 2017 November; Las Vegas, Nevada.	Study design does not meet our criteria for assessing efficacy
Irving P, Cummings F, Bloom SL, et al. Effect of Adalimumab on Patients with Moderate to Severe Ulcerative Colitis in UK Clinical Practice Setting: Results from Inspirada. Gut. 2016; 65 (S1): A86.	Study design does not meet our criteria for assessing efficacy

Kaeley GS, Nishio MJ, Goyal JR, et al. Changes in Ultrasonographic Vascularity Upon Initiation of Adalimumab Combination Therapy in Rheumatoid Arthritis Patients With an Inadequate Response to Methotrexate. Arthritis Rheumatol. 2016 Nov;68(11):2584-2592.	Study design does not meet our criteria for assessing efficacy
Kavanaugh A, van Vollenhoven RF, Fleischmann R, et al. Testing treat-to-target outcomes with initial methotrexate monotherapy compared with initial tumour necrosis factor inhibitor (adalimumab) plus methotrexate in early rheumatoid arthritis. Ann Rheum Dis. 2018 Feb;77(2):289-292.	Study design does not meet our criteria for assessing efficacy
Kavanaugh A, van Vollenhoven RF, Sunkureddi, et al. Disease Flares Among Early Rheumatoid Arthritis Patients Treated with Continued Methotrexate Either Alone or in Combination with Adalimumab (Humira). Arthritis Rheum. 2017 Sep; 69: 2456.	Study design does not meet our criteria for assessing efficacy
Keystone EC, Breedveld FC, van der Heijde D, et al. Achieving comprehensive disease control in patients with early and established rheumatoid arthritis treated with adalimumab plus methotrexate versus methotrexate alone. RMD Open. 2017 Sep 26;3(2):e000445.	Study design does not meet our criteria for assessing efficacy
Li N, Betts KA, Messali AJ, et al. Real-world Effectiveness of Biologic Disease-modifying Antirheumatic Drugs for the Treatment of Rheumatoid Arthritis After Etanercept Discontinuation in the United Kingdom, France, and Germany. Clin Ther. 2017 Aug;39(8):1618-1627.	Study design does not meet our criteria for assessing efficacy
Loftus EV Jr, 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. Inflamm Bowel Dis. 2019 Feb 8. doi: 10.1093/ibd/izz008. [Epub ahead of print]	Study design does not meet our criteria for assessing efficacy
Loftus EV, D'Haens GR, Reinisch W, et al. Adalimumab Long-Term Effectiveness in Adalimumab-Naïve Patients with Crohn's Disease: Final Data from Pyramid Registry. Gastroenterology. 2017 Apr 1;152(5):S743.	Study design does not meet our criteria for assessing efficacy
Loftus EV, Reinisch W, Panaccione R, et al. Long-Term Effectiveness and Safety of Adalimumab Based on Crohn's Disease Duration: Results from the Pyramid Registry. Gastroenterology. 2018 May 1;154(6):S403.	Study design does not meet our criteria for assessing efficacy
Loftus Jr E, D'Haens G, Reinisch W, et al. Adalimumab long-term effectiveness in adalimumab-naïve patients with Crohn's disease: final data from PYRAMID registry. J Crohns Colitis. 2017 Jan 26;11(suppl_1):S422-3.	Study design does not meet our criteria for assessing efficacy
Louis EJ, Reinisch W, Schwartz DA, et al. Adalimumab Reduces Extraintestinal Manifestations in Patients with Crohn's Disease: A Pooled Analysis of 11 Clinical Studies. Adv Ther. 2018 Apr;35(4):563-576.	Study design does not meet our criteria for assessing efficacy
Marin-Jimenez I, Casellas F, Esteve M, et al. Rapidity of onset of response to adalimumab in luminal Crohn's disease. Data from RAPIDA trial. J Crohns Colitis. 2017 Jan 26;11(S1):S395-6.	Study design does not meet our criteria for assessing efficacy
Mease PJ, Kavanaugh A, Coates LC, et al. Prediction and benefits of minimal disease activity in patients with psoriatic arthritis and active skin disease in the ADEPT trial. RMD Open. 2017 Jul 18;3(1):e000415.	Study design does not meet our criteria for assessing efficacy
Merola J, Sundaram M, Yang M, et al. Adalimumab is associated with reduced risk of joint-related signs and symptoms compared with methotrexate in	Study design does not meet our criteria for assessing efficacy

patients with moderate to severe psoriasis. J Am Acad Dermatol. 2016 May 1;74(5): AB235.	
Panaccione R, Colombel JF, Bossuyt P, et al. Tight Control for Crohn's Disease with Adalimumab Treatment is Cost Effective Over 48 Weeks: An Economic Assessment of the CALM Trial. Presented at 25th United European Gastroenterology Week. 2017 October-November; Barcelona, Spain.	Study design does not meet our criteria for assessing efficacy
Panaccione R, Löfberg R, Rutgeerts P, et al. Efficacy and Safety of Adalimumab by Disease Duration: Analysis of Pooled Data From Crohn's Disease Studies. J Crohns Colitis. 2019 May 27;13(6):725-734.	Study design does not meet our criteria for assessing efficacy
Papp K, Gooderham M, Lynde C, et al. Adding Methotrexate to Adalimumab Therapy Improved Treatment Efficacy and Quality of Life in Psoriasis Patients. Presented at 27th European Academy of Dermatology and Venereology Congress (EADV). 2018 September; Paris, France.	Study design does not meet our criteria for assessing efficacy
Papp K, Sundaram M, Yang M, et al. Psoriasis plaque resolution by body region and plaque signs with adalimumab and etanercept: An indirect comparison. J Am Acad Dermatol. 2016 May 1;74(5): AB264.	Study design does not meet our criteria for assessing efficacy
Papp KA, Yang M, Sundaram M, et al. Comparison of Adalimumab and Etanercept for the Treatment of Moderate to Severe Psoriasis: An Indirect Comparison Using Individual Patient Data from Randomized Trials. Value Health. 2018 Jan;21(1):1-8.	Study design does not meet our criteria for assessing efficacy
Pappas DA, Karki C, Shan Y, et al. Methotrexate Discontinuation from Combination Therapy with Adalimumab Is Not Associated with Inferior Outcomes at 6 Months. Arthritis Rheum. 2017 Oct; 69: 2453.	Study design does not meet our criteria for assessing efficacy
Pappas DA, Kremer JM, Griffith J, et al. Long-Term Effectiveness of Adalimumab in Patients with Rheumatoid Arthritis: An Observational Analysis from the Corrona Rheumatoid Arthritis Registry. Rheumatol Ther. 2017 Dec;4(2):375-389.	Study design does not meet our criteria for assessing efficacy
Pappas DA, Reed GW, Karki C, et al. Real-World Consistency of Response to Adalimumab over Time in Patients with Rheumatoid Arthritis: Results from the Corrona Registry. Arthritis Rheum. 2017 Oct; 69: 2454.	Study design does not meet our criteria for assessing efficacy
Philipp S, Pinter A, Unnebrink K, et al. Efficacy and Safety of Adalimumab and Methotrexate by Body Mass Index in Pediatric Patients with Chronic, Severe Psoriasis. Pediatr Dermatol. 2017 July; 34 (S1): S88.	Study design does not meet our criteria for assessing efficacy
Qiao Y, Winthrop KL, Griffith J, et al. Effects of adalimumab initiation on corticosteroid utilisation and medical costs among patients with rheumatoid arthritis. Ann Rheum Dis. 2018 June; 77 (S2): 523.	Study design does not meet our criteria for assessing efficacy
Reinisch W, Panaccione R, D'Haens G, et al. PYRAMID Registry: Long-term Safety and Effectiveness of Adalimumab by Baseline Immunomodulator Use in Patients With Crohn's Disease: 694. Am J Gastroenterol. 2017 Oct 1;112:S384.	Study design does not meet our criteria for assessing efficacy
Ryan C, Sundaram M, Yang M, et al J. Predicting PASI90 response among adalimumab-treated patients with moderate to severe psoriasis: 2571. J Am Acad Dermatol. 2016 May 1;74(5): AB263.	Study design does not meet our criteria for assessing efficacy

Smolen J, Fleischmann R, Aletaha D, et al. The identification of an ACR score with the optimal discriminatory ability between treatments in patients with early and established rheumatoid arthritis. Arthritis Rheum. 2016 Oct; 68: 497.	Study design does not meet our criteria for assessing efficacy
Smolen JS, Kavanaugh A, Aletaha D, et al. The Impact of Early Treatment with Adalimumab on Rheumatoid Factor and Anti-Citrullinated Peptide Antibody Levels in Patients with Rheumatoid Arthritis in The Optima Trial. Ann Rheum Dis. 2016 June; 75 (S2): THU0135.	Study design does not meet our criteria for assessing efficacy
Smolen JS, van Vollenhoven RF, Wolfe BA, et al. Adalimumab (HUMIRA) Halts Radiographic Progression and Reduces Disease Activity in Patients with a Poor Initial Response to Methotrexate. Arthritis Rheum. 2016 Oct; 68: 593.	Study design does not meet our criteria for assessing efficacy
Strand V, Betts KA, Mittal M, et al. Comparative Effectiveness of Adalimumab versus Secukinumab for the Treatment of Psoriatic Arthritis: A Matching-Adjusted Indirect Comparison. Rheumatol Ther. 2017 Dec;4(2):349-362.	Study design does not meet our criteria for assessing efficacy
Strand V, Betts KA, Mittal M, et al. Comparative Effectiveness of Adalimumab versus Secukinumab for the Treatment of Psoriatic Arthritis: A Matching-Adjusted Indirect Comparison. Rheumatol Ther. 2017 Dec;4(2):349-362.	Study design does not meet our criteria for assessing efficacy
Thaci D, Seyger MM, Unnebrink K, et al Efficacy and Safety of Adalimumab by Prior Treatment in Pediatric Patients with Chronic, Severe Psoriasis. Pediatr Dermatol. 2017 July; 34 (S1): S88-S89.	Study design does not meet our criteria for assessing efficacy
Travis S, Feagan B, Peyrin-Biroulet L, et al. Effect of adalimumab dose escalation on clinical, health-related quality of life, treatment satisfaction and work productivity outcomes among patients with ulcerative colitis in a clinical practice setting: results from INSPIRADA. J Crohn's Colitis. 2017 Jan 26;11(S1):S244-5.	Study design does not meet our criteria for assessing efficacy
Travis S, Feagan B, Peyrin-Biroulet L, et al. Effect of adalimumab on extraintestinal manifestations among patients with ulcerative colitis in a clinical practice setting. J Crohns Colitis. 2017 Feb 1;11(S1): S36.	Study design does not meet our criteria for assessing efficacy
Travis S, Feagan BG, Peyrin-Biroulet L, et al. Adalimumab Improves Treatment Satisfaction With Medication and Work Productivity Among Patients With Ulcerative Colitis in a Clinical Practice Setting: Results From INSPIRADA. Gastroenterology. 2016 Apr 1;150(4):S633.	Study design does not meet our criteria for assessing efficacy
Travis S, Feagan BG, Peyrin-Biroulet L, et al. Effect Of Adalimumab On Clinical And Health-related Quality Of Life Outcomes By Disease Severity And Prior Tumour Necrosis Factor Inhibitor Use In Patients With Ulcerative Colitis In A Clinical Practice Setting: Subgroup Analyses From InspirADA. Presented at 26th European Academy of Dermatology and Venereology Congress (EADV). 2017 September; Geneva, Switzerland.	Study design does not meet our criteria for assessing efficacy
Travis S, Feagan BG, Peyrin-Biroulet L, et al. Effect of Adalimumab on Clinical Outcomes and Health-related Quality of Life Among Patients With Ulcerative Colitis in a Clinical Practice Setting: Results From InspirADA. J Crohns Colitis. 2017 Oct 27;11(11):1317-1325.	Study design does not meet our criteria for assessing efficacy
Wang S, Jakubanis R, Piercy J, Skup M. Health-related quality of life, work productivity, and satisfaction with treatment amongst inflammatory bowel disease patients receiving adalimumab mono-versus adalimumab combo-therapy. J Crohns Colitis. 2016 Mar; 10: S388.	Study design does not meet our criteria for assessing efficacy

Wang S, Piercy J, Jakubanis R, Skup M. Satisfaction With Treatment Among IBD Patients Receiving Subcutaneous Biologic Treatment and Infused Biologic Treatment. Presented at the 11th Congress of the European Crohn's and Colitis Organization (ECCO). 2016 March; Amsterdam, the Netherlands.	Study design does not meet our criteria for assessing efficacy
Yagiz B, Coskun BN, Kiraz S, et al. Corticosteroid Utilization before and after Initiation of Biologic Dmards between Patients with Rheumatoid Arthritis. Arthritis Rheum. 2018; 70: 627.	Study design does not meet our criteria for assessing efficacy

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

Appendix B. Lyrica

Figure B1. PRISMA Flow Chart Showing Results of Literature Search for Lyrica

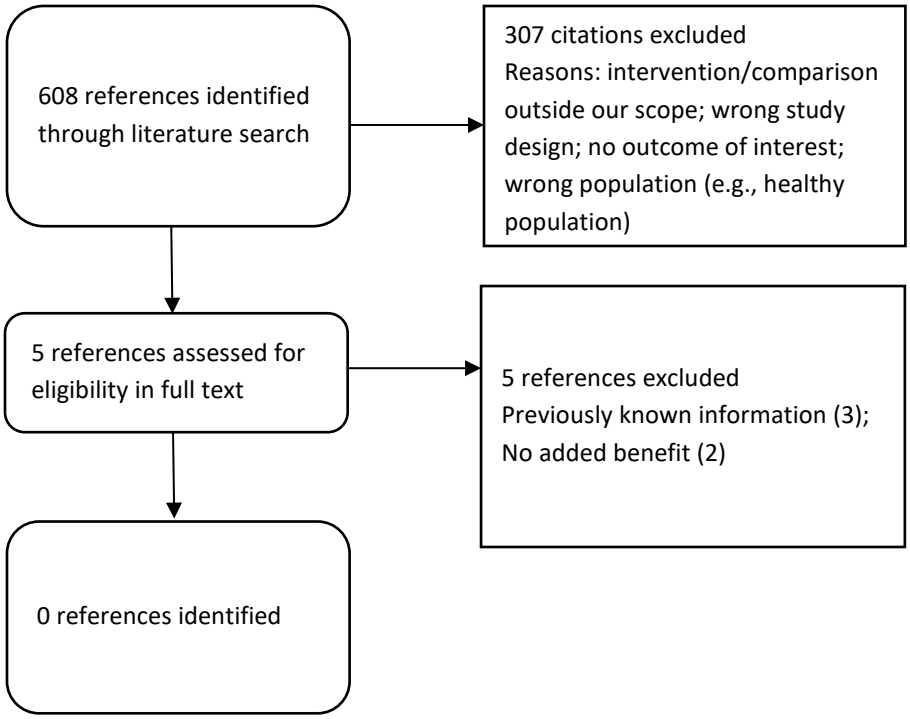

Table B1. Search Strategy of Lyrica in EMBASE

#1	'pregabalin':ab,ti OR 'lyrica':ab,ti
#2	'randomized controlled trial'/exp OR 'controlled clinical trial'/exp OR random*:ti,ab OR placebo:ti,ab OR 'drug therapy':lnk OR trial:ti,ab OR groups:ti,ab
#3	'clinical article'/exp OR 'controlled study'/exp OR 'major clinical study'/exp OR 'prospective study'/exp OR 'cohort analysis'/exp OR 'cohort':ti,ab OR 'compar*':ti,ab OR 'groups':ti,ab OR 'case control':ti,ab OR 'multivariate':ti,ab
#4	#2 OR #3
#5	#1 AND #4
#6	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
#7	#5 NOT #6
#8	#7 AND [english]/lim
#9	#8 AND [2016-2018]/py
#10	#9 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)

Appendix C. Genvoya

Table C1. Reasons for Exclusion

Citation	Reasons for Exclusion
Gupta SK, Post FA, Arribas JR, et al. Renal safety of TAF vs TDF or ABC in a pooled analysis of 27 phase 2/3 clinical trials. In: Presented at: 22nd international AIDS conference; July 23–27 2018, Amsterdam, The Netherlands. Abstract TUPEB113.	Previously known information related to safety
Gupta SK, Post FA, Arribas JR, et al. Renal safety of tenofovir alafenamide vs. tenofovir disoproxil fumarate: a pooled analysis of 26 clinical trials. AIDS. 2019 Jul 15;33(9):1455-1465.	Previously known information related to safety
Huhn GD, Tebas P, Gallant J, et al. A Randomized, Open-Label Trial to Evaluate Switching to Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Plus Darunavir in Treatment-Experienced HIV-1-Infected Adults. J Acquir Immune Defic Syndr. 2017 Feb 1;74(2):193-200.	Study design does not meet our criteria for assessing efficacy
Gaur A, Natukunda E, Kosalarksa P, et al. Pharmacokinetics, safety, and efficacy of E/C/F/TAF in HIV-1-infected children (6 to <12 years). Poster presented at the Conference on Retroviruses and Opportunistic Infections (CROI) 2017. Seattle, Washington. Poster #424.	Study design does not meet our criteria for assessing efficacy
Hines D, Ding Y, Wade R, et al. Persistence Among Treatment-Naive HIV-1 Patients: Single Versus Multiple Tablet Regimen Comparison. J Manag Care Spec Pharm. 2017 October; 23 (10A): S22.	Outcomes not relevant to our scope
Cohen J, Beaubrun A, Bashyal R, et al. Real-world persistence for newly prescribed HIV-1 treatment: Single versus multiple tablet regimen comparison. Pharmacoepidemiol Drug Saf. 2018 August; 27 (S2): 39.	Outcomes not relevant to our scope
Teira R, Romero A, Roca B, et al. Real-world persistence of E/C/F/TAF versus DTG+ ABC/3TC regimens for treatment of HIV in a large Spanish cohort: VACH. J Int AIDS Soc. 2018 October; 21 (S8): 66.	Outcomes not relevant to our scope
Rieke A, Jessen H, Pauli R, et al. Real-world effects of treatment with emtricitabine/tenofovir alafenamide versus emtricitabine/tenofovir disoproxil fumarate-based regimens in people living with HIV in a clinical cohort in Germany. J Int AIDS Soc. 2018 October; 21 (S8): 137.	Previously known information related to safety
Gallant J, Altice F, Folse HJ. Cost-consequences analysis of coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide in patient populations with differing risk profiles. Value Health. 2016 May ;19(3):A214.	Outcomes not relevant to our scope
Eron JJ Jr, Lelievre JD, Kalayjian R, et al. Safety of elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide in HIV-1-infected adults with end-stage renal disease on chronic haemodialysis: an open-label, single-arm, multicentre, phase 3b trial. Lancet HIV. 2018 Dec 13. pii: S2352-3018(18)30296-0.	Indication accounts for less than 10% of use

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

Appendix D. Truvada

Table D1. Reasons for Exclusion

Citation	Reason for Exclusion
Sullivan PS, Smith DK, Mera-Giler R, et al. The impact of pre-exposure prophylaxis with FTC/TDF on HIV diagnoses, 2012-2016, United States. Presented at 22nd international AIDS conference. 2018 July; Amsterdam, The Netherlands. Abstract LBPEC036.	Study design does not meet our criteria for assessing efficacy
Baeten J, Grant R, McCormack S, et al. HIV incidence in persons using Truvada (FTC/TDF) for HIV pre-exposure prophylaxis (PrEP): worldwide experience from 46 studies. AIDS Res Hum Retrov. 2018 October; 34 (S1): 79.	Study design does not meet our criteria for assessing efficacy
Marcus JL, Hurley LB, Hare CB, et al. HIV preexposure prophylaxis: Adherence and discontinuation in clinical practice. Poster presented at the Conference on Retroviruses and Opportunistic Infections (CROI) 2016. 2016 February. Boston, Massachusetts. Poster # 894	Outcomes not relevant to our scope
Mayer KH, Levine K, Maloney K,et al. Increasing HIV Suppression, PrEP Use and STDs in Boston MSM Accessing Primary Care. Poster presented at the Conference on Retroviruses and Opportunistic Infections (CROI) 2016. 2016 February. Boston, Massachusetts. Poster # 890.	Study design does not meet our criteria for assessing efficacy
Cohen J, Beaubrun A, Ding Y, Hines D. Estimation of the incremental lifetime cost of HIV compared to a HIV-uninfected population. HIV DART & Emerging Viruses. 2018 November: 78.	Outcomes not relevant to our scope
Chou J, Skornicki M, Bendavid E, Diaz O. Estimating the potential impact of PrEP uptake scenarios on the HIV epidemic in the United States. Poster presented at 22nd International AIDS Conference. July 23-27, 2018. Amsterdam, The Netherlands.	Outcomes not relevant to our scope
Drabo EF, Hay JW, Vardavas R, et al. A Cost-effectiveness Analysis of Preexposure Prophylaxis for the Prevention of HIV Among Los Angeles County Men Who Have Sex With Men. Clin Infect Dis. 2016 Dec 1;63(11):1495-1504.	Outcomes not relevant to our scope
Shen M, Xiao Y, Rong L, et al. The cost-effectiveness of oral HIV pre-exposure prophylaxis and early antiretroviral therapy in the presence of drug resistance among men who have sex with men in San Francisco. BMC Med. 2018 Apr 24;16(1):58.	Outcomes not relevant to our scope
McKenney J, Chen A, Hoover KW, et al. Optimal costs of HIV pre-exposure prophylaxis for men who have sex with men. PLoS One. 2017 Jun 1;12(6):e0178170.	Outcomes not relevant to our scope
Elion R, Altice F, Mayer K, et al. Impact of Targeted PreExposure Prophylaxis Strategies for Men who Have Sex with Men (MSM) in the United States. IAS Conference on HIV Science (IAS 2017); 2017 Jul; page 474.	Study design does not meet our criteria for assessing efficacy
Jenness SM, Goodreau SM, Rosenberg E, et al. Impact of the Centers for Disease Control's HIV Preexposure Prophylaxis Guidelines for Men Who Have Sex With Men in the United States. J Infect Dis. 2016 Dec 15;214(12):1800-1807.	Study design does not meet our criteria for assessing efficacy

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

Appendix E. Rituxan

Table E1. Reasons for Exclusion

Citation	Reasons for Exclusion
Joly P, Maho-Vaillant M, Prost-Squarcioni C, et al; French study group on autoimmune bullous skin diseases. First-line rituximab combined with short-term prednisone versus prednisone alone for the treatment of pemphigus (Ritux 3): a prospective, multicentre, parallel-group, open-label randomised trial. Lancet. 2017 May 20;389(10083):2031-2040.	Indication accounts for less than 10% of use
Terrier B, Pagnoux C, Perrodeau É, et al; French Vasculitis Study Group. Long-term efficacy of remission-maintenance regimens for ANCA-associated vasculitides. Ann Rheum Dis. 2018 Aug;77(8):1150-1156.	Indication accounts for less than 10% of use
Rummel MJ, Koenigsmann M, Chow KU, et al. Two years rituximab maintenance vs. observation after first line treatment with bendamustine plus rituximab (B-R) in patients with marginal zone lymphoma (MZL): Results of a prospective, randomized, multicenter phase 2 study (the StiL NHL7-2008 MAINTAIN trial). J Clin Oncol. 2018 May; 36 (15S): 7515.	Indication accounts for less than 10% of use
Gottenberg JE, Brocq O, Perdriger A, et al. Non-TNF-Targeted Biologic vs a Second Anti-TNF Drug to Treat Rheumatoid Arthritis in Patients With Insufficient Response to a First Anti-TNF Drug: A Randomized Clinical Trial. JAMA. 2016 Sep 20;316(11):1172-1180.	Intervention/ comparison not relevant to scope
Taverna C, Martinelli G, Hitz F, et al. Rituximab Maintenance for a Maximum of 5 Years After Single-Agent Rituximab Induction in Follicular Lymphoma: Results of the Randomized Controlled Phase III Trial SAKK 35/03. J Clin Oncol. 2016 Feb 10;34(5):495-500.	Intervention/ comparison outside our scope
Watanabe T, Tobinai K, Wakabayashi M, et al; JCOG0203 Collaborators. Outcomes after R-CHOP in patients with newly diagnosed advanced follicular lymphoma: a 10-year follow-up analysis of the JCOG0203 trial. Lancet Haematol. 2018 Nov;5(11):e520-e531.	Intervention/ comparison outside our scope
Rummel M, Buske C, Hertenstein B, et al. Four versus two years of Rituximab maintenance (R-maintenance) following Bendamustine plus Rituximab (B-R): initial results of a prospective, randomized multicenter phase 3 study in first-line follicular lymphoma (the StiL NHL7-2008 MAINTAIN study). Blood. 2017; 130 (S1): 483	Intervention/ comparison outside our scope
Watanabe T, Tobinai K, Wakabayashi M, et al. Ten-year follow-up of newly diagnosed follicular lymphoma patients treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) as first-line therapy in JCOG0203 trial. Blood. 2017;130 (S1): 5168.	Intervention/ comparison outside our scope
Srour SA, Li S, Popat UR, et al. A randomized phase II study of standard-dose versus high-dose rituximab with BEAM in autologous stem cell transplantation for relapsed aggressive B-cell non-hodgkin lymphomas: long term results. Br J Haematol. 2017 Aug;178(4):561-570.	Intervention/ comparison outside our scope

Pfreundschuh M, Murawski N, Zeynalova S, et al. Optimization of rituximab for the treatment of DLBCL: increasing the dose for elderly male patients. Br J Haematol. 2017 Nov;179(3):410-420.	Intervention/ comparison outside our scope
Ferreri AJM, Sassone M, Zaja F, et al. Lenalidomide Maintenance Significantly Improves Survival Figures in Patients with Relapsed Diffuse Large B-Cell Lymphoma (rDLBCL) Who Are Not Eligible for Autologous Stem Cell Transplantation (ASCT): Final Results of a Multicentre Phase II Trial. Blood. 2016; 128 (22): 474.	Intervention/ comparison outside our scope
Strati P, Sivina M, Kim E, et al. Achievement of complete remission (CR) as an endpoint for patients with chronic lymphocytic leukemia (CLL) treated with ibrutinib. J Clin Oncol. 2018 May; 36 (15S): 7522.	Abstract - limited information on study design
Gottenberg J-E, Morel J, Constantin A, et al. Corticosteroid sparing effect of non-TNF targeted biologics, rituximab, abatacept and tocilizumab in common practice: Data from 3183 patients enrolled in the French society of rheumatology registries. Arthritis Rheum. 2017; 69: hal-01670657.	Outcomes not relevant to our scope
Gómez-Puerta JA, Zapata ND, Gonzalez LA, et al. Efficacy and survival of biologic DMARD therapies as monotherapy: Real world data. Arthritis Rheum. 2017; 69 (S10): 2489	Intervention/ comparison outside our scope
Woyach JA, Ruppert AS, Heerema NA, et al. Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL. N Engl J Med. 2018 Dec 27;379(26):2517-2528.	New evidence of no clinical improvement with rituximab
Goede V, Fischer K, Dyer MJ, et al. Overall survival benefit of obinutuzumab over rituximab when combined with chlorambucil in patients with chronic lymphocytic leukemia and comorbidities: Final survival analysis of the CLL11 study. HemaSphere. 2018; 2: 30	New evidence of no improvement in efficacy in the rituximab arm
Shadman M, Li H, Rimsza L, et al. Continued Excellent Outcomes in Previously Untreated Patients With Follicular Lymphoma After Treatment With CHOP Plus Rituximab or CHOP Plus (131)I-Tositumomab: Long-Term Follow-Up of Phase III Randomized Study SWOG-S0016. J Clin Oncol. 2018 Mar 1;36(7):697-703.	New evidence of no improvement in efficacy in the rituximab arm
Huang X, Qiu L, Jin J, et al. Ibrutinib versus rituximab in relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma: a randomized, open-label phase 3 study. Cancer Med. 2018 Apr;7(4):1043-1055.	New evidence of no improvement in efficacy in the rituximab arm
Marcus R, Davies A, Ando K, et al. Obinutuzumab for the First-Line Treatment of Follicular Lymphoma. N Engl J Med. 2017 Oct 5;377(14):1331-1344.	New evidence of no improvement in efficacy in the rituximab arm
Maloney DG, Fukuhara N, Ogura M, et al. A phase III study of ofatumumab vs rituximab in indolent B-cell non-Hodgkin lymphoma relapsed after rituximab containing therapy (HOMER): Results of the interim analysis. Haematologica. 2016;101:102	New evidence of no improvement in efficacy in the rituximab arm
Davies A, Trask P, Demeter J, et al. Health-related quality of life results from the phase III gallium study of obinutuzumab-based and rituximab-based therapy in patients with previously untreated advanced indolent non-Hodgkin lymphoma. Haematologica. 2017;102:190-1	New evidence of no improvement in efficacy in the rituximab arm

Gerlag D, Safy M, Maijer K, et al. Prevention of rheumatoid arthritis by B cell directed therapy in the earliest phase of the disease: The prairi study. Ann Rheum Dis. 2016;75:125-6	New evidence of no improvement in efficacy in the rituximab arm
Gerlag DM, Safy M, Maijer KI, et al. Effects of B-cell directed therapy on the preclinical stage of rheumatoid arthritis: the PRAIRI study. Ann Rheum Dis. 2019 Feb;78(2):179-185.	New evidence of no improvement in efficacy in the rituximab arm
Hiddemann W, Barbui AM, Canales Albendea MA, et al. Immunochemotherapy with obinutuzumab or rituximab in previously untreated follicular lymphoma in the randomized phase III gallium study: Analysis by chemotherapy regimen. Haematologica. 2017;102:314	New evidence of no improvement in efficacy in the rituximab arm
Burger JA, Sivina M, Ferrajoli A, et al. Randomized trial of ibrutinib versus ibrutinib plus rituximab (IB+R) in patients with chronic lymphocytic leukemia (CLL). Blood. 2017;130 (S1): 427.	New evidence of no improvement in efficacy in the rituximab arm
Choquette D, Bessette L, Haraoui B, et al. Rituximab shows better sustainability than TNF inhibitors when used following initial biologic DMARD failure in the treatment of rheumatoid arthritis: 8 years of real-world observations from the RHUMADATA® clinical database and registry. Ann Rheum Dis. 2017;76:845-6.	Outcomes not relevant to our scope
Gottenberg J-E, Morel J, Constantin A, et al. Monotherapy with abatacept, rituximab or tocilizumab is not associated with a significantly lower long term retention than combination with synthetic DMARD: Long-term registry data in 4498 real-life patients with rheumatoid arthritis. Arthritis Rheum. 2016;68:2006-8	Outcomes not relevant to our scope
Dartigeas C, Van Den Neste E, Léger J, et al; CLL 2007 SA investigators; French Innovative Leukemia Organization (FILO). Rituximab maintenance versus observation following abbreviated induction with chemoimmunotherapy in elderly patients with previously untreated chronic lymphocytic leukaemia (CLL 2007 SA): an open-label, randomised phase 3 study. Lancet Haematol. 2018 Feb;5(2):e82-e94.	Previously known information about rituximab related to efficacy
Salles GA, Seymour JF, Feugier P, et al. Long term follow-up of the PRIMA study: Half of patients receiving rituximab maintenance remain progression free at 10 years. Blood. 2017; 130 (S1): 486.	Previously known information about rituximab related to efficacy
Halwani AS, Rasmussen K, Patil V, et al. Maintenance rituximab after first line treatment in veterans with follicular lymphoma is associated with prolonged overall survival. Blood. 2017; 130 (S1): 1489.	Previously known information about rituximab related to efficacy
Hill BT, Nastoupil L, Winter AM, et al. Maintenance rituximab or observation after frontline treatment with bendamustine-rituximab (br) for follicular lymphoma: A real world analysis across 13 US cancer centers. Blood. 2017;130 (S1): 2779.	Previously known information about rituximab related to efficacy
Zhou X, Ma T, Zhang Y, et al. Rituximab maintenance therapy for patients with diffuse large B-cell lymphoma: A meta-analysis. PLoS One. 2017 Mar 29;12(3):e0174648.	Previously known information about rituximab related to efficacy

Barta SK, Li H, Hochster HS, et al. Randomized phase 3 study in low-grade lymphoma comparing maintenance anti-CD20 antibody with observation after induction therapy: A trial of the ECOG-ACRIN Cancer Research Group (E1496). Cancer. 2016 Oct;122(19):2996-3004.	Previously known information about rituximab related to efficacy
Greil R, Obrtlíková P, Smolej L, et al. Rituximab maintenance versus observation alone in patients with chronic lymphocytic leukaemia who respond to first-line or second-line rituximab-containing chemoimmunotherapy: final results of the AGMT CLL-8a Mabtenance randomised trial. Lancet Haematol. 2016 Jul;3(7):e317-29.	Previously known information about rituximab related to efficacy
Marzolini MAV, Qian W, Clifton-Hadley L, et al. Quality of life in advanced-stage, asymptomatic, nonbulky follicular lymphoma treated with rituximab shows significant improvement compared with watchful-waiting: Phase 3 randomised international study. HemaSphere. 2018;2:655-6	Previously known information about rituximab related to efficacy
Peterfy C, Emery P, Tak PP, et al. MRI assessment of suppression of structural damage in patients with rheumatoid arthritis receiving rituximab: results from the randomised, placebo-controlled, double-blind RA-SCORE study. Ann Rheum Dis. 2016 Jan;75(1):170-7.	Previously known information about rituximab related to efficacy
Behrens F, Rossmanith T, Köhm M, et al. Rituximab in combination with leflunomide: Results from a multicenter randomized placebo controlled investigator initiated clinical trial in active rheumatoid arthritis (AMARA-study). Ann Rheum Dis. 2016;75:502	Previously known information about rituximab related to efficacy
Maloney DG, Fukuhara N, Ogura M, et al. A phase III study of ofatumumab vs rituximab in indolent B-cell non-Hodgkin lymphoma relapsed after rituximab containing therapy (HOMER): Results of the interim analysis. Haematologica. 2016;101:102	Previously known information about rituximab related to efficacy
Barta SK, Li H, Hochster HS, et al. Randomized phase 3 study in low-grade lymphoma comparing maintenance anti-CD20 antibody with observation after induction therapy: A trial of the ECOG-ACRIN Cancer Research Group (E1496). Cancer. 2016 Oct;122(19):2996-3004.	Previously known information about rituximab related to efficacy
Thompson P, Keating M, O'Brien S, et al. Lenalidomide and rituximab in combination as initial treatment of chronic lymphocytic leukemia: Initial results of a phase II study. Leuk Lymphoma. 2014;56:160-1	Previously known information about rituximab related to efficacy
Wijesinghe H, Galappatthy P, de Silva R, et al. Leflunomide is equally efficacious and safe compared to low dose rituximab in refractory rheumatoid arthritis given in combination with methotrexate: results from a randomized double blind controlled clinical trial. BMC Musculoskelet Disord. 2017 Jul 19;18(1):310.	Previously known information about rituximab related to efficacy
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Silva-Fernández L, De Cock D, Lunt M, et al. Serious infection risk after 1 year between patients with rheumatoid arthritis treated with rituximab or with a second TNFi after initial TNFi failure: results from The British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Rheumatology (Oxford). 2018 Sep 1;57(9):1533-1540.	Previously known information about rituximab related to safety
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Raynauld JP, Bessette L, Brown J, et al. Use of rituximab compared to anti-TNF agents as second and third-line therapy in patients with rheumatoid arthritis. A 6-year follow-up report from the rhumadata® clinical database and registry. Ann Rheum Dis. 2016;75:190	Previously known information about rituximab related to safety
Gottenberg J-E, Morel J, Constantin A, et al. Long-term registry data in 4498 patients with rheumatoid arthritis indicate a similar safety but a different drug retention between abatacept, rituximab and tocilizumab. Arthritis and Rheumatology. 2016;68:2550-3	Previously known information about rituximab related to safety
Gottenberg J-E, Morel J, Constantin A, et al. Similar rates of death, serious infections, cancers, major cardiovascular events in patients treated with abatacept, rituximab and tocilizumab: Long-term registry data in 4498 patients with rheumatoid arthritis. Arthritis and Rheumatology. 2016;68:3536-7	Previously known information about rituximab related to safety
Morschhauser F, Fowler NH, Feugier P, et al; RELEVANCE Trial Investigators. Rituximab plus Lenalidomide in Advanced Untreated Follicular Lymphoma. N Engl J Med. 2018 Sep 6;379(10):934-947.	Rituximab in all comparison arms
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Chiappella A, Martelli M, Angelucci E, et al. Rituximab-dose-dense chemotherapy with or without high-dose chemotherapy plus autologous stem-cell transplantation in high-risk diffuse large B-cell lymphoma (DLCL04): final results of a multicentre, open-label, randomised, controlled, phase 3 study. Lancet Oncol. 2017 Aug;18(8):1076-1088.	Rituximab in all comparison arms

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Lamy T, Damaj G, Soubeyran P, et al; LYSA Group. R-CHOP 14 with or without radiotherapy in nonbulky limited-stage diffuse large B-cell lymphoma. Blood. 2018 Jan11;131(2):174-181.	Rituximab in all comparison arms
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Dührsen U, Broszeit-Luft S, Dieing A, et al. Rituximab maintenance therapy of follicular lymphoma in clinical practice. Cancer Med. 2018;7(7):2903-12	Rituximab in all comparison arms
Cencini E, Puccini B, Rigacci L, et al. Radiotherapy plus rituximab as first-line regimen for localized follicular lymphoma. Leuk Lymphoma. 2018 Jun;59(6):1420-1426.	Rituximab in all comparison arms
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Procházka V, Papajík T, Janíková A, et al. Frontline intensive chemotherapy improves outcome in young, high-risk patients with follicular lymphoma: pair-matched analysis from the Czech Lymphoma Study Group Database. Leuk Lymphoma. 2017 Mar;58(3):601-613.	Rituximab in all comparison arms
Evens AM, Hong F, Habermann TM, et al. A 3-arm randomized phase ii trial with bendamustine/rituximab therapy in untreated high risk (HR) follicular lymphoma (FL): Bortezomib induction or novel IMID continuation (BIONIC) study from the ECOG-ACRIN cancer research group. Blood. 2017;130 (S1): 482.	Rituximab in all comparison arms
Coleman M, Andorsky DJ, Yacoub A, et al. Phase IIIb study of lenalidomide plus rituximab followed by maintenance in relapsed or refractory NHL: Analysis of marginal zone lymphoma. Hematol Oncol. 2017;35 (S2):148	Rituximab in all comparison arms
Burke JM, Andorsky DJ, Yacoub A, et al. Phase IIIB randomized study of lenalidomide plus rituximab (R2) followed by lenalidomide vs. rituximab maintenance in patients with relapsed/refractory NHL: Analysis of follicular lymphoma patients. Haematologica. 2017;102:249-50	Rituximab in all comparison arms
Zinzani PL, Topp MS, Yuen SLS, et al. Phase 2 study of venetoclax plus rituximab or randomized ven plus bendamustine+rituximab (BR) versus BR in patients with relapsed/refractory follicular lymphoma: Interim data. Blood. 2016;128(22): 617.	Rituximab in all comparison arms
Kimby E, Martinelli G, Ostenstad B, et al. Rituximab plus lenalidomide improves the complete remission rate in comparison with rituximab monotherapy in untreated follicular lymphoma patients in need of therapy. Primary endpoint analysis of the randomized phase-2 trial SAKK 35/10. Blood. 2014;124(21): 799.	Rituximab in all comparison arms
Kesavan M, Turner JH, McQuillan AD. Long-term outcomes of 131I-rituximab radioimmunotherapy in follicular non-hodgkin lymphoma: Ten year update on toxicity, time-to-next-treatment and survivial of the phase ii initial study. Haematologica. 2016;101:274-5	Rituximab in all comparison arms
Casadei B, Pellegrini C, Pulsoni A, et al. 90-yttrium-ibritumomab tiuxetan consolidation of fludarabine, mitoxantrone, rituximab in intermediate/high-risk follicular lymphoma: updated long-term results after a median follow-up of 7 years. Cancer Med. 2016 Jun;5(6):1093-7.	Rituximab in all comparison arms
de Vos S, Swinnen LJ, Wang D,et al. Venetoclax, bendamustine, and rituximab in patients with relapsed or refractory NHL: a phase Ib dose-finding study. Ann Oncol. 2018 Sep 1;29(9):1932-1938.	Rituximab in all comparison arms

Leonard JP, Kolibaba KS, Reeves JA, et al. Randomized Phase II Study of R-CHOP With or Without Bortezomib in Previously Untreated Patients With Non-Germinal Center B-Cell-Like Diffuse Large B-Cell Lymphoma. J Clin Oncol. 2017 Nov 1;35(31):3538-3546.	Rituximab in all comparison arms
Kuruvilla J, Crump M, Villa D, et al. Canadian Cancer Trials Group (CCTG) LY.17: A Randomized Phase II Study Evaluating Novel Salvage Therapy Pre-Autologous Stem Cell Transplant (ASCT) in Relapsed/Refractory Diffuse Large B Cell Lymphoma (RR-DLBCL)- Outcome of Ibrutinib + R-GDP. Hematol Oncol. 2017;35(S2):88	Rituximab in all comparison arms
González-Barca E, Carrillo-Cruz E, Grande C, et al. Phase 2 randomized trial comparing standard RCHOP versus brcap (bortezomib, rituximab, cyclophosphamide, adriamycin and prednisone) as first line treatment in young patients with high-risk diffuse large B-cell lymphoma (DLBCL). A study from Spanish group geltamo. Blood. 2016;128(22): 4201.	Rituximab in all comparison arms
Shanafelt TD, Wang V, Kay NE, et al. A randomized phase III study of ibrutinib (PCI-32765)-based therapy vs. standard fludarabine, cyclophosphamide, and rituximab (FCR) chemoimmunotherapy in untreated younger patients with chronic lymphocytic leukemia (CLL): A trial of the ECOG-ACRIN cancer research group (E1912). Blood. 2018;132 (S1): LBA-4	Rituximab in all comparison arms
Deng R, Gibiansky L, Lu T, et al. Exposure-response analysis of venetoclax in combination with rituximab in patients with relapsed or refractory chronic lymphocytic leukemia: Phase 3 murano study. Clin Pharm Drug Dev. 2018;7:13-4	Rituximab in all comparison arms
Byrd JC, Ruppert AS, Heerema NA, et al. Lenalidomide consolidation benefits patients with CLL receiving chemoimmunotherapy: results for CALGB 10404 (Alliance). Blood Adv. 2018 Jul 24;2(14):1705-1718.	Rituximab in all comparison arms
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Munir T, Howard DR, McParland L, et al. Results of the randomized phase IIB ADMIRE trial of FCR with or without mitoxantrone in previously untreated CLL. Leukemia. 2017 Oct;31(10):2085-2093.	Rituximab in all comparison arms
Howard DR, Munir T, McParland L, et al. Results of the randomized phase IIB ARCTIC trial of low-dose rituximab in previously untreated CLL. Leukemia. 2017 Nov;31(11):2416-2425.	Rituximab in all comparison arms
Zent CS, Victoria Wang X, Ketterling RP, et al. A phase II randomized trial comparing standard and low dose rituximab combined with alemtuzumab as initial treatment of progressive chronic lymphocytic leukemia in older patients: a trial of the ECOG-ACRIN cancer research group (E1908). Am J Hematol. 2016 Mar;91(3):308-12.	Rituximab in all comparison arms
Robak T, Błoński J, Skotnicki AB, et al. Rituximab, cladribine, and cyclophosphamide (RCC) induction with rituximab maintenance in chronic lymphocytic leukemia: PALG - CLL4 (ML21283) trial. Eur J Haematol. 2018 May;100(5):465-474.	Previously known information about rituximab related to efficacy

Harrold LR, John A, Best J, et al. Impact of rituximab on patient-reported outcomes in patients with rheumatoid arthritis from the US Corrona Registry. Clin Rheumatol. 2017 Sep;36(9):2135-2140.	Study design does not meet our criteria for assessing efficacy
Berger JR, Malik V, Lacey S, et al. Progressive multifocal leukoencephalopathy in rituximab-treated rheumatic diseases: a rare event. J Neurovirol. 2018 Jun;24(3):323-331.	Study design does not meet our criteria for assessing efficacy
Brown S, Everett CC, Naraghi K, et al. Alternative tumour necrosis factor inhibitors (TNFi) or abatacept or rituximab following failure of initial TNFi in rheumatoid arthritis: the SWITCH RCT. Health technology assessment (Winchester, England). 2018;22(34):1-280	Study design does not meet our criteria for assessing efficacy
Zhang H-Q, Lin X, Shen X-L. Rituximab therapy and increased risk of side effects in patients with relapsed lymphomas: A meta-analysis. Int J Clin Exp Med. 2017;10(2):2684-94	Study design does not meet our criteria for assessing efficacy
Vidal L, Gafter-Gvili A, Salles G, et al. Rituximab maintenance improves overall survival of patients with follicular lymphoma-Individual patient data meta-analysis. Eur J Cancer. 2017 May;76:216-225.	Previously known information about rituximab related to efficacy
Nastoupil LJ, Westin JR, Fowler NH, et al. Response rates with pembrolizumab in combination with rituximab in patients with relapsed follicular lymphoma: Interim results of an on open-label, phase II study. J Clin Oncol. 2017;35(15S): 7519.	Study design does not meet our criteria for assessing efficacy
Nastoupil LJ, Westin J, Fowler N, et al. High response rates with pembrolizumab in combination with rituximab in patients with relapsed follicular lymphoma: Interim results of an on open-label, phase II study. Hematol Oncol. 2017;35:120-1	Study design does not meet our criteria for assessing efficacy
Matasar M, Herrera AF, Kamdar M, et al. Polatuzumab vedotin plus bendamustine and rituximab or obinutuzumab in relapsed/refractory follicular lymphoma or diffuse large B-cell lymphoma: Updated results of a phase 1B/2 study. Haematologica. 2017;102:173	Abstract – limited information on study design
Martin P, Jung SH, Pitcher B, et al. A phase II trial of lenalidomide plus rituximab in previously untreated follicular non-Hodgkin's lymphoma (NHL): CALGB 50803 (Alliance). Ann Oncol. 2017 Nov 1;28(11):2806-2812.	Study design does not meet our criteria for assessing efficacy
Hill BT, Nastoupil L, Winter AM, et al. Maintenance rituximab or observation after frontline treatment with bendamustine-rituximab (br) for follicular lymphoma: A real world analysis across 13 US cancer centers. Blood. 2017;130 (S1): 2779.	Abstract – limited information on study design
Bari A, Marcheselli R, Marcheselli L, et al; Gruppo Italiano Studio Linfomi (GISL). A Multicenter Phase II Study of Twice-Weekly Bortezomib plus Rituximab in Patients with Relapsed Follicular Lymphoma: Long-Term Follow-Up. Acta Haematol. 2017;137(1):7-14.	Study design does not meet our criteria for assessing efficacy
Ruella M, Filippi AR, Bruna R, et al. Addition of Rituximab to Involved-Field Radiation Therapy Prolongs Progression-free Survival in Stage I-II Follicular Lymphoma: Results of a Multicenter Study. Int J Radiat Oncol Biol Phys. 2016 Mar 15;94(4):783-91.	Study design does not meet our criteria for assessing efficacy

Párraga FJP, Navarro JAM, Nieto SD, et al. Response-adapted treatment with rituximab/bendamustine/mitoxantrone/dexamethasone and maintenance therapy with rituximab in patients with follicular lymphoma in relapse or refractory to first-line treatment with immunochemotherapy: RBMDGELTAMO08 trial. Blood. 2016;128(22): 1788.	Study design does not meet our criteria for assessing efficacy
Illidge TM, McKenzie HS, Mayes S, et al. Short duration immunochemotherapy followed by radioimmunotherapy consolidation is effective and well tolerated in relapsed follicular lymphoma: 5-year results from a UK National Cancer Research Institute Lymphoma Group study. Br J Haematol. 2016 Apr;173(2):274-82.	Study design does not meet our criteria for assessing efficacy
Evens AM, Hong F, Habermann TM, et al. Effect of bortezomib on complete remission (CR) rate when added to bendamustine-rituximab (BR) in previously untreated high-risk (HR) follicular lymphoma (FL): A randomized phase II trial of the ECOG-ACRIN Cancer Research Group (E2408). J Clin Oncol. 2016;34(15S):7507.	Study design does not meet our criteria for assessing efficacy
Barr PM, Li H, Burack R, et al. Sequential RCHOP, radioimmunotherapy and rituximab maintenance improves early outcomes in advanced stage follicular lymphoma: 5 Year outcomes from SWOG 0801. Blood. 2016;128(22): 614.	Study design does not meet our criteria for assessing efficacy
Younes A, Burke JM, Cheson B, et al. Safety and efficacy of atezolizumab in combination with rituximab plus chop in previously untreated patients with diffuse large B-cell lymphoma (DLBCL): Primary analysis of a phase I/II study. Blood. 2018;132 (S1): 2969.	Study design does not meet our criteria for assessing efficacy
Storti S, Spina M, Pesce EA, et al. Rituximab plus bendamustine as front-line treatment in frail elderly (>70 years) patients with diffuse large B-cell non-Hodgkin lymphoma: a phase II multicenter study of the Fondazione Italiana Linfomi. Haematologica. 2018 Aug;103(8):1345-1350.	Study design does not meet our criteria for assessing efficacy
Salles GA, Jurczak W, Andorsky DJ, et al. Results of a Phase 3 Randomised Multicenter Study Comparing Pixantrone + Rituximab with Gemcitabine + Rituximab in Patients with Relapsed Aggressive B-Cell Non-Hodgkin Lymphoma Not Eligible for Stem Cell Transplantation. Blood. 2018;132(S1):4189	Rituximab in all comparison arms
Castellino A, Chiappella A, LaPlant BR, et al. Lenalidomide plus R-CHOP21 in newly diagnosed diffuse large B-cell lymphoma (DLBCL): long-term follow-up results from a combined analysis from two phase 2 trials. Blood Cancer J. 2018 Nov 8;8(11):108.	Study design does not meet our criteria for assessing efficacy
Cabannes-Hamy A, Peyrade F, Jardin F, et al; LYSA; lymphoma study association. Central nervous system relapse in patients over 80 years with diffuse large B-cell lymphoma: an analysis of two LYSA studies. Cancer Med. 2018 Mar;7(3):539-548.	Study design does not meet our criteria for assessing efficacy
Rozental A, Gafter-Gvilli A, Vidal-Fisher L, et al. The role of maintenance therapy in patients with diffuse large b-cell lymphoma: A systematic review and meta-analysis. Blood. 2017;130 (S1): 4117.	Study design does not meet our criteria for assessing efficacy
Oki Y, Kelly KR, Flinn I, et al. CUDC-907 in relapsed/refractory diffuse large B-cell lymphoma, including patients with MYC-alterations: results from an expanded phase I trial. Haematologica. 2017 Nov;102(11):1923-1930.	Study design does not meet our criteria for assessing efficacy

Karmali R, Larson ML, Shammo JM, et al. Phase 2 study of CHOP-R-14 followed by (90)Y-ibritumomab tiuxetan in patients with previously untreated diffuse large B-cell lymphoma. Mol Clin Oncol. 2017 Apr;6(4):627-633.	Study design does not meet our criteria for assessing efficacy
Kalpadakis C, Pangalis G, Vassilakopoulos T, et al. Splenic marginal zone lymphoma (SMZL) treated with rituximab (R) monotherapy: A long term follow-up study on 104 patients. Haematologica. 2017;102:147	Study design does not meet our criteria for assessing efficacy
Feng J, Wu J, Song Y, al. Three-year follow-up on safety and effectiveness of rituximab plus chemotherapy as first-line treatment of diffuse large B-cell lymphoma. Blood. 2017;130 (S1): 5208.	Study design does not meet our criteria for assessing efficacy
Doorduijn JK, van Imhoff GW, van der Holt B, et al. Treatment of secondary central nervous system lymphoma with intrathecal rituximab, high-dose methotrexate, and R-DHAP followed by autologous stem cell transplantation: results of the HOVON 80 phase 2 study. Hematol Oncol. 2017 Dec;35(4):497-503.	Study design does not meet our criteria for assessing efficacy
Advani RH, Lebovic D, Chen A, et al. Phase I Study of the Anti-CD22 Antibody-Drug Conjugate Pinatuzumab Vedotin with/without Rituximab in Patients with Relapsed/Refractory B-cell Non-Hodgkin Lymphoma. Clin Cancer Res. 2017 Mar 1;23(5):1167-1176.	Study design does not meet our criteria for assessing efficacy
Yoon DH, Sohn BS, Hong JY, et al. Phase 2 study of abbreviated 3 cycles of rituximab plus CHOP (cyclophosphamide, adriamycin, vincristine, and prednisolone) immunochemotherapy in patients with completely excised stage i or II CD20+ diffuse large B-cell lymphoma (CISL 12-09). Blood. 2016;128(22): 4193.	Study design does not meet our criteria for assessing efficacy
Ghesquieres H, Houillier C, Chinot O, et al. Rituximab-lenalidomide (REVRI) in relapse or refractory primary central nervous system (PCNSL) or vitreo retinal lymphoma (PVRL): Results of a "proof of concept" phase II study of the French loc network. Blood. 2016;128(22): 785.	Study design does not meet our criteria for assessing efficacy
Tadmor T, Herishanu Y, Braester A, et al. Results of a phase II of low-dose fludarabine and cyclophosphamide combined with standard dose rituximab (FCR-LITE) in elderly, untreated patients with chronic lymphocytic leukemia (CLL): The Israeli CLL Study Group Experience. Blood. 2018;132 (S1): 5566.	Study design does not meet our criteria for assessing efficacy
Reiser M, Dörfel S, Hensel M, et al. Rituximab in combination with chemotherapy for the treatment of chronic lymphocytic leukaemia in clinical practice. Eur J Haematol. 2018 May;100(5):455-464.	Study design does not meet our criteria for assessing efficacy
Egle A, Steurer M, Melchardt T, et al. Fludarabine and rituximab with escalating doses of lenalidomide followed by lenalidomide/rituximab maintenance in previously untreated chronic lymphocytic leukaemia (CLL): the REVLIRIT CLL-5 AGMT phase I/II study. Ann Hematol. 2018 Oct;97(10):1825-1839.	Study design does not meet our criteria for assessing efficacy
Appleby N, O'Brien D, Quinn FM, et al. Risk adjusted therapy in chronic lymphocytic leukemia: a phase II cancer trials Ireland (CTRIAL-IE [ICORG 07-01]) study of fludarabine, cyclophosphamide, and rituximab therapy evaluating response adapted, abbreviated frontline therapy with FCR in non-del(17p) CLL. Leuk Lymphoma. 2018 Jun;59(6):1338-1347.	Study design does not meet our criteria for assessing efficacy

Al-Sawaf O, Bahlo J, Robrecht S, et al. Outcome of patients aged 80 years or older treated for chronic lymphocytic leukaemia. Br J Haematol. 2018 Dec;183(5):727-735.	Study design does not meet our criteria for assessing efficacy
Jain P, Keating MJ, Wierda WG, et al. Long-term Follow-up of Treatment with Ibrutinib and Rituximab in Patients with High-Risk Chronic Lymphocytic Leukemia. Clin Cancer Res. 2017 May 1;23(9):2154-2158.	Study design does not meet our criteria for assessing efficacy
Hillmen P, Badoux X, Delgado J, et al. Safety results of terminated phase 2 study of idelalisib plus rituximab in treatment naive chronic lymphocytic leukemia (CLL) with del(17P). Haematologica. 2017;102:172	Study design does not meet our criteria for assessing efficacy
Strati P, Thompson PA, Keating M, et al. A phase II study of the combination of lenalidomide and rituximab in patients with treatment-Naïve and relapsed chronic lymphocytic leukemia. Blood. 2016;128(22): 4389.	Study design does not meet our criteria for assessing efficacy
Städler N, Shang A, Bosch F, et al. A Systematic Review and Network Meta-Analysis to Evaluate the Comparative Efficacy of Interventions for Unfit Patients with Chronic Lymphocytic Leukemia. Adv Ther. 2016 Oct;33(10):1814-1830.	Study design does not meet our criteria for assessing efficacy
Shadman M, Sorror ML, Sandmaier BM, et al. Adding peri-transplant rituximab to non-myeloablative (NMA) conditioning before allogeneic hematopoietic cell transplantation (allo-HCT) to improve disease-related outcomes in patients with chronic lymphocytic leukemia (CLL): Phase II clinical trial. Journal of Clinical Oncology. 2016;34 (15S): 7052.	Study design does not meet our criteria for assessing efficacy
Maurer C, Pflug N, Bahlo J, et al; German CLL Study Group. Bendamustine and rituximab in combination with lenalidomide in patients with chronic lymphocytic leukemia. Eur J Haematol. 2016 Sep;97(3):253-60.	Study design does not meet our criteria for assessing efficacy
Han HJ, Lu YW, Xia RX. [Clinical Efficacy and Safety of Rituximab Combined with Fludarabine and Cyclophosphamide for Treatment of Chronic Lymphocytic Leukemia]. Zhongguo Shi Yan Xue Ye Xue Za Zhi. 2016 Feb;24(1):25-9.	Study design does not meet our criteria for assessing efficacy
Chavez JC, Piris-Villaespesa M, Dalia S, et al. Results of a phase II study of lenalidomide and rituximab for refractory/relapsed chronic lymphocytic leukemia. Leuk Res. 2016 Aug;47:78-83.	Study design does not meet our criteria for assessing efficacy
Rodriguez García SDLC, Castellanos-Moreira R, Hernandez-Miguel MV, et al. Safety of rituximab in patients with rheumatoid arthritis. Eleven-year follow-up observational study. Ann Rheum Dis. 2018;77:1394-5.	Study design does not meet our criteria for assessing efficacy
Oldroyd AGS, Symmons DPM, Sergeant JC, et al; BSRBR-RA Contributors Group. Long-term persistence with rituximab in patients with rheumatoid arthritis. Rheumatology (Oxford). 2018 Jun 1;57(6):1089-1096.	Study design does not meet our criteria for assessing efficacy
Murrell DF, Peña S, Joly P, et al. Diagnosis and Management of Pemphigus: recommendations by an International Panel of Experts. J Am Acad Dermatol. 2018 Feb 10. pii: S0190-9622(18)30207-X.	Study design does not meet our criteria for assessing efficacy
Henry J, Gottenberg JE, Rouanet S, et al; Auto-Immunity and Rituximab investigators. Doses of rituximab for retreatment in rheumatoid arthritis: influence on maintenance and risk of serious infection. Rheumatology (Oxford). 2018 Mar 1;57(3):538-547.	Study design does not meet our criteria for assessing efficacy
Ismajli M, Ionescu R, Moore S, Leandro M. Long-term use of rituximab in rheumatoid arthritis: 17 years follow-up. Rheumatology (United Kingdom). 2017;56:ii142	Study design does not meet our criteria for assessing efficacy

Vassilopoulos D, Delicha EM, Settas L, et al. Safety profile of repeated rituximab cycles in unselected rheumatoid arthritis patients: a long-term, prospective real-life study. Clin Exp Rheumatol. 2016 Sep-Oct;34(5):893-900.	Previously known information about rituximab related to safety
Sim DW, Park KH, Park HJ, et al. Clinical characteristics of adverse events associated with therapeutic monoclonal antibodies in Korea. Pharmacoepidemiol Drug Saf. 2016 Nov;25(11):1279-1286.	Study design does not meet our criteria for assessing efficacy
Scott FI, Mamtani R, Brensinger CM, et al. Risk of Nonmelanoma Skin Cancer Associated With the Use of Immunosuppressant and Biologic Agents in Patients With a History of Autoimmune Disease and Nonmelanoma Skin Cancer. JAMA Dermatol. 2016 Feb;152(2):164-72.	Study design does not meet our criteria for assessing efficacy
Gottenberg J-E, Ravaud P, Bardin T, et al. Safety of multiple retreatments with rituximab in real life: Long term registry data from 1984 patients with rheumatoid arthritis. Arthritis Rheum. 2016;68:3548-9	Study design does not meet our criteria for assessing efficacy
Gómez-Puerta JA, Uribe Botero L, Urrego J, et al. Survival and effectiveness of rituximab treatment in patients with rheumatoid arthritis in daily clinical practice. Ann Rheum Dis. 2016;75:1023-4	Study design does not meet our criteria for assessing efficacy
Porter D, van Melckebeke J, Dale J, et al. Tumour necrosis factor inhibition versus rituximab for patients with rheumatoid arthritis who require biological treatment (ORBIT): an open-label, randomised controlled, non-inferiority, trial. Lancet. 2016 Jul 16;388(10041):239-47.	Study population outside approved label indication
Danese MD, Reyes CM, Gleeson ML, et al. Estimating the Population Benefits and Costs of Rituximab Therapy in the United States from 1998 to 2013 Using Real-World Data. Med Care. 2016 Apr;54(4):343-9.	Outcomes not relevant to our scope

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

Appendix F. Neulasta

Table F1. Reasons for Exclusion

Citation	Reason for Exclusion
Weycker D, Bensink M, Lonshteyn A, et al. Risk of chemotherapy-induced febrile neutropenia by day of pegfilgrastim prophylaxis in US clinical practice from 2010 to 2015. Curr Med Res Opin. 2017 Dec;33(12):2107-2113.	Intervention/comparison outside our scope
Stephens JM, Li X, Reiner M, Tzivelekis S. Annual patient and caregiver burden of oncology clinic visits for granulocyte-colony stimulating factor therapy in the US. J Med Econ. 2016;19(5):537-47.	Outcomes not relevant to our scope
Stephens JM, Bensink M, Bowers C, Hollenbeak CS. Risks and consequences of travel burden on prophylactic granulocyte colony-stimulating factor administration and incidence of febrile neutropenia in an aged Medicare population. Curr Med Res Opin. 2019 Feb;35(2):229-240.	Intervention/comparison outside our scope
Weycker D, Li X, Figueredo J, et al. Risk of chemotherapy-induced febrile neutropenia in cancer patients receiving pegfilgrastim prophylaxis: does timing of administration matter? Support Care Cancer. 2016 May;24(5):2309-2316.	Intervention/comparison outside our scope
Li Y, Klippel Z, Shih X, et al. Trajectory of absolute neutrophil counts in patients treated with pegfilgrastim on the day of chemotherapy versus the day after chemotherapy. Cancer Chemother Pharmacol. 2016 Apr;77(4):703-12.	Intervention/comparison outside our scope
Weycker D, Hanau A, Lonshteyn A, et al. Risk of chemotherapy-induced febrile neutropenia with same-day versus next-day pegfilgrastim prophylaxis among patients aged ≥65 years: a retrospective evaluation using Medicare claims. Curr Med Res Opin. 2018 Sep;34(9):1705-1711.	Intervention/comparison outside our scope
Mahler LJ, DiBlasi R, Perez A, et al. On-Body Injector: An Administration Device for Pegfilgrastim. Clin J Oncol Nurs. 2017 Feb 1;21(1):121-122.	Intervention/comparison outside our scope
Lin J, Yucel A, Walker MS, et al. Effect of pegfilgrastim on-body injector (OBI) on cancer care: A real-world health system and interrupted time series analysis. J Clin Oncol. 2018 June; 36 (15S): e18859	Intervention/comparison outside our scope
Fust K, Parthan A, Maschio M, et al. Granulocyte colony-stimulating factors in the prevention of febrile neutropenia: review of cost-effectiveness models. Expert Rev Pharmacoecon Outcomes Res. 2017 Feb;17(1):39-52.	Outcomes not relevant to our scope
Hauber AB, Mange B, Price MA, et al. Administration options for pegfilgrastim prophylaxis: patient and physician preferences from a cross-sectional survey. Support Care Cancer. 2018 Jan;26(1):251-260.	Outcomes not relevant to our scope
Marion S, Tzivelekis S, Darden C, et al. "Same-Day" administration of pegfilgrastim following myelosuppressive chemotherapy: clinical practice and provider rationale. Support Care Cancer. 2016 Sep;24(9):3889-96.	Outcomes not relevant to our scope
Joshi RS, Egbuna OI, Cairns AS, et al. Performance of the pegfilgrastim on-body injector as studied with placebo buffer in healthy volunteers. Curr Med Res Opin. 2017 Feb;33(2):379-384.	Wrong population

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

Appendix G. Cialis

Figure G1. PRISMA Flow Chart Showing Results of Literature Search for Cialis

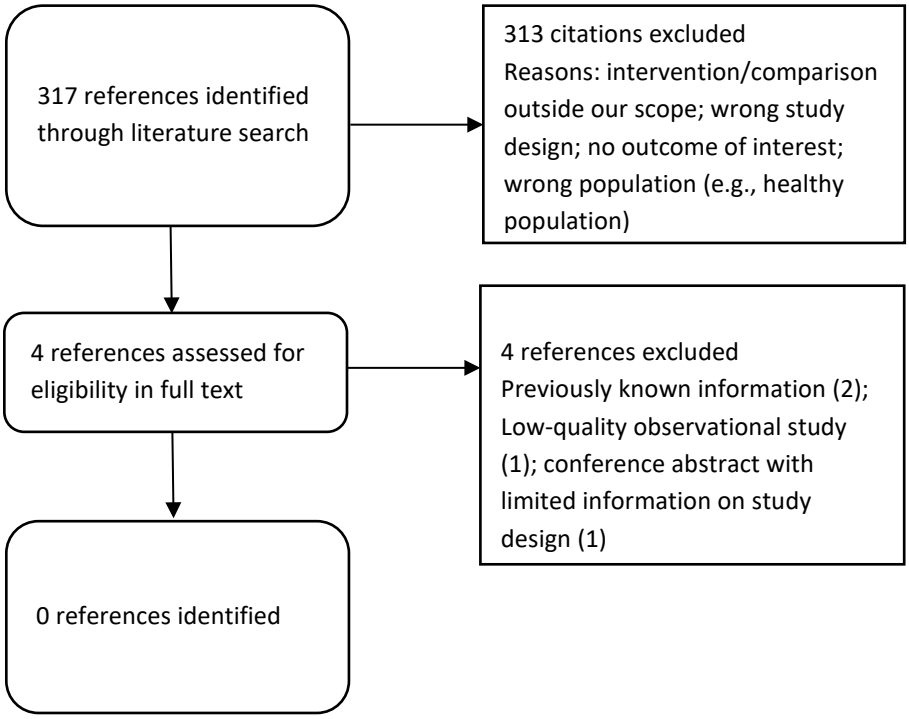

Table G1. Search Strategy of Cialis in EMBASE

#1	'tadalafil':ab,ti OR 'cialis':ab,ti
#2	'randomized controlled trial'/exp OR 'controlled clinical trial'/exp OR random*:ti,ab OR placebo:ti,ab OR 'drug therapy':lnk OR trial:ti,ab OR groups:ti,ab
#3	'clinical article'/exp OR 'controlled study'/exp OR 'major clinical study'/exp OR 'prospective study'/exp OR 'cohort analysis'/exp OR 'cohort':ti,ab OR 'compar*':ti,ab OR 'groups':ti,ab OR 'case control':ti,ab OR 'multivariate':ti,ab
#4	#2 OR #3
#5	#1 AND #4
#6	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
#7	#5 NOT #6
#8	#7 AND [english]/lim
#9	#8 AND [2016-2018]/py
#10	#9 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)

Appendix H. Tecfidera

Table H1. Reasons for Exclusion

Citation	Reasons for Exclusion
Chan A, Cutter G, Fox RJ, et al. Comparative effectiveness of delayed-release dimethyl fumarate versus glatiramer acetate in multiple sclerosis patients: results of a matching-adjusted indirect comparison. J Comp Eff Res. 2017 Jun;6(4):313-323.	Study design does not meet our criteria for assessing efficacy
Fox RJ, Chan A, Zhang A, et al. Comparative effectiveness using a matching-adjusted indirect comparison between delayed-release dimethyl fumarate and fingolimod for the treatment of multiple sclerosis. Curr Med Res Opin. 2017 Feb;33(2):175-183.	Study design does not meet our criteria for assessing efficacy
Kalincik T, Butzkueven H. Observational data: Understanding the real MS world. Mult Scler. 2016 Nov;22(13):1642-1648.	Study design does not meet our criteria for assessing efficacy
Braune S, Grimm S, van Hövell P, et al; NTD Study Group. Comparative effectiveness of delayed-release dimethyl fumarate versus interferon, glatiramer acetate, teriflunomide, or fingolimod: results from the German NeuroTransData registry. J Neurol. 2018 Dec;265(12):2980-2992.	Low-quality evidence
Buron MD, Chalmer TA, Sellebjerg F, et al. Comparative effectiveness of teriflunomide and dimethyl fumarate: A nationwide cohort study. Neurology. 2019 Apr 16;92(16):e1811-e1820.	Study published outside of the timeframe of our review
Boster A, Nicholas J, Wu N, et al. Comparative Effectiveness Research of Disease-Modifying Therapies for the Management of Multiple Sclerosis: Analysis of a Large Health Insurance Claims Database. Neurol Ther. 2017 Jun;6(1):91-102.	Low-quality observational study
Hersh CM, Love TE, Cohn S, et al. Comparative efficacy and discontinuation of dimethyl fumarate and fingolimod in clinical practice at 12-month follow-up. Mult Scler Relat Disord. 2016 Nov;10:44-52.	Previously known information about dimethyl fumarate related to efficacy
Hersh CM, Love TE, Bandyopadhyay A, et al. Comparative efficacy and discontinuation of dimethyl fumarate and fingolimod in clinical practice at 24-month follow-up. Mult Scler J Exp Transl Clin. 2017 Aug 24;3(3):2055217317715485.	Previously known information about dimethyl fumarate related to efficacy
Spelman T, Kalincik T, Trojano M, et al. Comparative analysis of MS outcomes in dimethyl fumarate-treated patients relative to propensity matched fingolimod, interferon, glatiramer acetate, or teriflunomide. Mult Scler J. 2016; 22: 602–603.	Abstract – limited information on study design
Vollmer B, Ontaneda D, Bandyopadhyay A, et al. Discontinuation and comparative effectiveness of dimethyl fumarate and fingolimod in 2 centers. Neurol Clin Pract. 2018 Aug;8(4):292-301.	Previously known information about dimethyl fumarate related to efficacy
Sattarnezhad N, Healy BC, Baharnoori M, et al. Dimethyl fumarate versus interferon for treatment of relapsing-remitting multiple Sclerosis. Neurology. 2017; 88(16 suppl): P6.381	Study design does not meet our criteria for assessing efficacy
Ontaneda D, Nicholas J, Carraro M, et al. Comparative effectiveness of dimethyl fumarate versus fingolimod and teriflunomide among MS patients switching	Study published outside of the timeframe of our review

from first-generation platform therapies in the US. Mult Scler Relat Disord. 2019 Jan;27:101-111.	
Nicholas J, Boster A, Wu N, et al. Comparison of Disease-Modifying Therapies for the Management of Multiple Sclerosis: Analysis of Healthcare Resource Utilization and Relapse Rates from US Insurance Claims Data. Pharmacoecon Open. 2018 Mar;2(1):31-41.	Low-quality observational study
Sloane J, Phillips JT, Calkwood J, et al. Delayed-release dimethyl fumarate demonstrated no difference in clinical outcomes versus fingolimod in patients with relapsing-remitting multiple sclerosis: results from the real-world EFFECT study. Mult Scler J. 2017 Oct; 23: 855-856	Previously known information about dimethyl fumarate related to efficacy
Chan A, Cohan S, Stark J, et al. Treatment with delayed-release dimethyl fumarate is associated with fewer relapses versus glatiramer acetate in patients with relapsing remitting multiple sclerosis: real-world comparative effectiveness analyses from the EFFECT study.Mult Scler J. 2017 Oct; 23: 611	Previously known information about dimethyl fumarate related to efficacy
Prosperini L, Lucchini M, Haggiag S, et al. Fingolimod vs dimethyl fumarate in multiple sclerosis: A real-world propensity score-matched study. Neurology. 2018 Jul 10;91(2):e153-e161.	Previously known information about dimethyl fumarate related to efficacy
Fox RJ, Gold R, Phillips JT, et al. Efficacy and Tolerability of Delayed-release Dimethyl Fumarate in Black, Hispanic, and Asian Patients with Relapsing-Remitting Multiple Sclerosis: Post Hoc Integrated Analysis of DEFINE and CONFIRM. Neurol Ther. 2017 Dec;6(2):175-187.	Study design does not meet our criteria for assessing efficacy
Calkwood J, Cohan S, Chan A, et al. Real-world Effectiveness of Delayed-release Dimethyl Fumarate in Relapsing-remitting Multiple Sclerosis Patients Who Are Treatment-naïve or Treated With Only One Prior Therapy: Final Results from the EFFECT Study. Neurology. 2018 April; 90 (15 Supplement): 373.	Study design does not meet our criteria for assessing efficacy
Giles K, Balashov K, Jones CC, et al. Real-world Efficacy of Delayed-Release Dimethyl Fumarate in Early Multiple Sclerosis: Interim Results from ESTEEM. Mult Scler J. 2018; 24: 595.	Study design does not meet our criteria for assessing efficacy
Kresa-Reahl K, Repovic P, Robertson D, et al. Effectiveness of Delayed-release Dimethyl Fumarate on Clinical and Patient-reported Outcomes in Patients With Relapsing Multiple Sclerosis Switching From Glatiramer Acetate: RESPOND, a Prospective Observational Study. Clin Ther. 2018 Dec;40(12):2077-2087.	Study design does not meet our criteria for assessing efficacy
Oshima Y, Tanimoto T, Yuji K, Tojo A. Drug-associated progressive multifocal leukoencephalopathy in multiple sclerosis patients. Mult Scler. 2019 Jul;25(8):1141-1149.	Study design does not meet our criteria for assessing efficacy
Lee A, Pike J, Edwards MR, et al. Quantifying the Benefits of Dimethyl Fumarate Over β Interferon and Glatiramer Acetate Therapies on Work Productivity Outcomes in MS Patients. Neurol Ther. 2017 Jun;6(1):79-90.	Study design does not meet our criteria for assessing efficacy
Zipoli V, Tortorella P, Goretti B, et al. Effect of delayed-release dimethyl fumarate on cognition in Italian patients with relapsing remitting multiple sclerosis: the phase 4 StarTec study. Mult Scler J. 2018; 24: 198-199	Study design does not meet our criteria for assessing efficacy
Fox RJ, Chan A, Gold R, et al. Characterizing absolute lymphocyte count profiles in dimethyl fumarate-treated patients with MS: Patient management considerations. Neurol Clin Pract. 2016 Jun;6(3):220-229.	Study design does not meet our criteria for assessing efficacy

Fox RJ, Chan A, Gold R, et al. Absolute lymphocyte count and lymphocyte subset profiles during long-term treatment with delayed-release dimethyl fumarate in patients with relapsing-remitting multiple sclerosis. Mult Scler J. 2016; 22: 349.	Study design does not meet our criteria for assessing efficacy
Giles K, Hanna J, Wu F, et al. Efficacy of Delayed-Release Dimethyl Fumarate in Newly Diagnosed and Other Early Multiple Sclerosis Patients, and Patients Switching from Interferon or Glatiramer Acetate, in Routine Medical Practice: Interim Results from ESTEEM. Neurology. 2018 April; 90 (15S): P1. 367	Study design does not meet our criteria for assessing efficacy
Hersh C, Harris H, Cohn S, et al. Comparative effectiveness and discontinuation of dimethyl fumarate and fingolimod in clinical practice at 36-month follow-up. Mult Scler J. 2018 October; 24: 266.	Previously known information about dimethyl fumarate related to efficacy
Kresa-Reahl K, Repovic P, Robertson D, Okwuokenye M, Meltzer L, Mendoza J. Clinical measures and impact on patient-reported outcomes of delayed-release dimethyl fumarate in relapsing multiple sclerosis patients after suboptimal response to glatiramer acetate: analysis of the 12-month RESPOND study. Mult Scler J. 2016; 22: 774	Study design does not meet our criteria for assessing efficacy
Gold R, Giovannoni G, Phillips T, et al. Delayed-release Dimethyl Fumarate demonstrates sustained efficacy over nine years in newly diagnosed patients with relapsing-remitting multiple Sclerosis. Revue Neurologique. 2019 Apr; 175: S101.	Study design does not meet our criteria for assessing efficacy

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

Appendix I. Revlimid

Table I1. Reasons for Exclusion

Citation	Reasons for Exclusion
Attal M, Palumbo A, Holstein SA, et al. Lenalidomide (LEN) maintenance (MNTC) after high-dose melphalan and autologous stem cell transplant (ASCT) in multiple myeloma (MM): A meta-analysis (MA) of overall survival (OS). J Clin Oncol. 2016 May; 34 (15S): 8001.	Previously known information about lenalidomide related to efficacy
Fenk R, Giagounidis A, Goldschmidt H, et al. Maintenance therapy (MT) with 25 versus 5 mg lenalidomide (Len) after prolonged Len consolidation therapy (CT) in newly-diagnosed, transplant-eligible patients (pts) with multiple myeloma (MM). J Clin Oncol. 2018 May; 36 (15S): 8016.	Lenalidomide in all comparison arms
Gay F, De Paoli L, Larocca A, et al. Lenalidomide-Prednisone vs Lenalidomide Alone Maintenance In Newly Diagnosed Multiple Myeloma: Individual Patient Data Meta-Analysis Of 2 Randomized Phase III Trials. HemaSphere. 2018 June; 2 (S1): 590-591.	Lenalidomide in all comparison arms
Goldschmidt H, Mai EK, Dürig J, et al. Response-adapted lenalidomide maintenance in newly diagnosed, transplant-eligible multiple myeloma: results from the multicenter phase III GMMG-MM5 trial. Blood. 2017 130 (S1): 400.	Lenalidomide in all comparison arms
Jackson GH, Davies FE, Pawlyn C, et al; UK NCRI Haemato-oncology Clinical Studies Group. Lenalidomide maintenance versus observation for patients with newly diagnosed multiple myeloma (Myeloma XI): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2019 Jan;20(1):57-73.	Previously known information about lenalidomide related to efficacy
McCarthy PL, Holstein SA, Petrucci MT, et al. Lenalidomide Maintenance After Autologous Stem-Cell Transplantation in Newly Diagnosed Multiple Myeloma: A Meta-Analysis. J Clin Oncol. 2017 Oct 10;35(29):3279-3289.	Previously known information about lenalidomide related to efficacy
Schmitz S, Buchanan V, Leahy J, et al. A Systematic Review and Network Meta-Analysis of Maintenance Treatment for Patients with Newly Diagnosed Multiple Myeloma Post-Autologous Stem Cell Transplant. Blood. 2017; 130 (S1): 1832	Previously known information about lenalidomide related to efficacy
Solovev MV, Mendeleeva LP, Firsova MV, et al. Efficacy of Maintenance Therapy Following Auto-HSCT Depending on MRD Status in Patients with Multiple Myeloma. Blood. 2018; 132 (S1): 3432	Previously known information about lenalidomide related to efficacy
Somlo G, Pasquini MC, Blackwell B, et al. Response status as predictor of survival after autologous hematopoietic cell transplant (AHCT), without or with consolidation (with bortezomib, lenalidomide (Len) and dexamethasone) and len maintenance (AM vs. ACM) versus tandem AHCT and len maintenance (TAM) for up-front treatment of patients (pts) with multiple myeloma (MM): BMT CTN0702-stamina (NCT01109004). J Clin Oncol. 2017 May; 35 (15S): 8010	Study design does not meet our criteria for assessing efficacy

Sonneveld P, Beksac M, van der Holt B, et al. Consolidation followed by maintenance therapy versus maintenance alone in newly diagnosed, transplant eligible patients with multiple myeloma (MM): A randomized phase 3 study of the European Myeloma Network (EMN02/HO95 MM Trial). Blood. 2016; 128 (22): 242.	Lenalidomide in all comparison arms
Stadtmauer EA, Pasquini MC, Blackwell B, et al. Comparison of autologous hematopoietic cell transplant (autoHCT), bortezomib, lenalidomide (Len) and dexamethasone (RVD) consolidation with Len maintenance, tandem Autohct with Len maintenance (TAM) and Autohct with Len maintenance (AM) for up-front treatment of patients with multiple myeloma (MM): primary results from the randomized phase III trial of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN 0702 - StaMINA Trial). Blood. 2016;128(22):LBA-1.	Previously known information about lenalidomide related to efficacy
Zweegman S, van der Holt B, Mellqvist UH, et al. Melphalan, prednisone, and lenalidomide versus melphalan, prednisone, and thalidomide in untreated multiple myeloma. Blood. 2016 Mar 3;127(9):1109-16.	Previously known information about lenalidomide related to efficacy
Attal M, Lauwers-Cances V, Hulin C, et al; IFM 2009 Study. Lenalidomide, Bortezomib, and Dexamethasone with Transplantation for Myeloma. N Engl J Med. 2017 Apr 6;376(14):1311-1320.	Study design does not meet our criteria for assessing efficacy
Bringhen S, Offidani M, Musto P, et al. Long term outcome of lenalidomide-dexamethasone (Rd) vs melphalan-lenalidomide-prednisone (MPR) vs cyclophosphamide-prednisone-lenalidomide (CPR) as induction followed by lenalidomide-prednisone (RP) vs lenalidomide (R) as maintenance in a community-based newly diagnosed myeloma population: updated analysis of EMN01 phase III study. Blood. 2017; 130 (S1): 901	Study design does not meet our criteria for assessing efficacy
Cavo M, Palumbo A, Zweegman S, et al. Upfront autologous stem cell transplantation (ASCT) versus novel agent-based therapy for multiple myeloma (MM): a randomized phase 3 study of the European Myeloma Network (EMN02/HO95 MM trial). J Clin Oncol. 2016 May; 34 (15S): 8000.	Intervention/comparison outside our scope
Durie BG, Hoering A, Abidi MH, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. Lancet. 2017 Feb 4;389(10068):519-527.	Lenalidomide in all comparison arms
Facon T, Dimopoulos MA, Dispenzieri A, et al. Final analysis of survival outcomes in the phase 3 FIRST trial of up-front treatment for multiple myeloma. Blood. 2018 Jan 18;131(3):301-310.	Previously known information about lenalidomide related to efficacy
Gay FM, Foà R, Musto P, et al. Updated efficacy data and MRD analysis according to risk status in newly diagnosed myeloma patients treated with carfilzomib+ lenalidomide or cyclophosphamide (FORTE trial). J Clin Oncol. 2018 May; 36 (15S): 8009.	Outcomes not relevant to our scope
Gay F, Oliva S, Petrucci MT, et al. Autologous transplant vs oral chemotherapy and lenalidomide in newly diagnosed young myeloma patients: a pooled analysis. Leukemia. 2017 Aug;31(8):1727-1734.	Previously known information about

	lenalidomide related to efficacy
Jackson GH, Davies FE, Pawlyn C, et al. A Quadruplet Regimen Comprising Carfilzomib, Cyclophosphamide, Lenalidomide, Dexamethasone (KCRD) Vs an Immunomodulatory Agent Containing Triplet (CTD/CRD) Induction Therapy Prior to Autologous Stem Cell Transplant: Results of the Myeloma XI Study. Blood. 2018; 132 (S1): 302.	Abstract – limited information on study design
Knop S, Langer C, Engelhardt MM, et al. Lenalidomide, doxorubicin hydrochloride and dexamethasone versus bortezomib, lenalidomide, and dexamethasone prior to scheduled stem cell transplant in newly diagnosed myeloma. J Clin Oncol. 2017 May; 35 (15S): 8001.	Lenalidomide in all comparison arms
Mateos MV, Hernández MT, Giraldo P, et al. Lenalidomide plus dexamethasone versus observation in patients with high-risk smouldering multiple myeloma (QuiRedex): long-term follow-up of a randomised, controlled, phase 3 trial. Lancet Oncol. 2016 Aug;17(8):1127-1136.	Study population outside approved label indication
Magarotto V, Bringhen S, Offidani M, et al. Triplet vs doublet lenalidomide-containing regimens for the treatment of elderly patients with newly diagnosed multiple myeloma. Blood. 2016 Mar 3;127(9):1102-8.	Lenalidomide in all comparison arms
Mookerjee A, Gupta R, Jasrotia S, et al. Bortezomib, Lenalidomide and Low-Dose Dexamethasone (VRD) Versus Lenalidomide and Low-Dose Dexamethasone (Ld) for Newly-Diagnosed Multiple Myeloma-a Randomized Phase III Study. Blood. 2017; 130 (S1): 906	Lenalidomide in all comparison arms
Pawlyn C, Davies F, Cairns D, et al. Quadruplet vs sequential triplet induction Therapy for myeloma patients: results of the MYELOMA XI study. Haematologica. 2017 June; 102: 142.	Outcomes not relevant to our scope
Ramasamy K, Thom H, D'Souza VK, et al. Relative Efficacy of Treatment Options in Newly Diagnosed Multiple Myeloma: Results from a Systematic Literature Review and Network Meta-Analysis. Blood. 2018; 132 (S1): 4744	Previously known information about lenalidomide related to efficacy
Remya S, Sudha MJ, Nair RB, Jayakumar KL. A prospective comparative study of safety of lenalidomide plus dexamethasone combination therapy versus VAD (vincristine, doxorubicin and dexamethasone) regimen in the treatment of multiple myeloma. International Journal of Pharmaceutical Sciences and Research. 2017 Nov 1;8(11):4645-52.	Previously known information about lenalidomide related to safety
Bahlis N, Dimopoulos MA, White DJ, et al. Three-Year Follow up of the Phase 3 Pollux Study of Daratumumab Plus Lenalidomide and Dexamethasone (D-Rd) Versus Lenalidomide and Dexamethasone (Rd) Alone in Relapsed or Refractory Multiple Myeloma (RRMM). Blood. 2018; 132 (S1): 1996.	Lenalidomide in all comparison arms
Mateos MV, Masszi T, Grzasko N, et al. Impact of prior therapy on the efficacy and safety of oral ixazomib-lenalidomide-dexamethasone vs. placebo-lenalidomide-dexamethasone in patients with relapsed/refractory multiple myeloma in TOURMALINE-MM1. Haematologica. 2017 Oct;102(10):1767-1775.	Lenalidomide in all comparison arms
Dimopoulos MA, Stewart AK, Masszi T, et al. Carfilzomib-lenalidomide-dexamethasone vs lenalidomide-dexamethasone in relapsed multiple myeloma by previous treatment. Blood Cancer J. 2017 Apr 21;7(4):e554.	Lenalidomide in all comparison arms

Dimopoulos MA, Lonial S, Betts KA, et al. Elotuzumab plus lenalidomide and dexamethasone in relapsed/refractory multiple myeloma: Extended 4-year follow-up and analysis of relative progression-free survival from the randomized ELOQUENT-2 trial. Cancer. 2018 Oct 15;124(20):4032-4043.	Lenalidomide in all comparison arms
Dimopoulos M, Wang M, Maisnar V, et al. Response and progression-free survival according to planned treatment duration in patients with relapsed multiple myeloma treated with carfilzomib, lenalidomide, and dexamethasone (KRd) versus lenalidomide and dexamethasone (Rd) in the phase III ASPIRE study. J Hematol Oncol. 2018 Apr 4;11(1):49.	Lenalidomide in all comparison arms
Dimopoulos MA, San-Miguel J, Belch A, et al. Daratumumab plus lenalidomide and dexamethasone versus lenalidomide and dexamethasone in relapsed or refractory multiple myeloma: updated analysis of POLLUX. Haematologica. 2018 Dec;103(12):2088-2096.	Lenalidomide in all comparison arms
Facon T, Kumar SK, Plesner T, et al. Phase 3 randomized study of daratumumab plus lenalidomide and dexamethasone (D-Rd) versus lenalidomide and dexamethasone (Rd) in patients with newly diagnosed multiple myeloma (NDMM) ineligible for transplant (MAIA). Blood. 2018; 132 (S1): LBA-2.	Lenalidomide in all comparison arms
Garderet L, Laubach JP, Stoppa AM, et al. Longer Time to Best Response and Depth of Response Are Associated with Improved Duration of Best Achieved Response and Progression-Free Survival (PFS): Post-Hoc Analysis of Phase 3 Tourmaline-MM1 Trial in Relapsed/Refractory Multiple Myeloma (RRMM). 2016; 128 (22): 2134.	Lenalidomide in all comparison arms
Hou J, Jin J, Xu Y, et al. Randomized, double-blind, placebo-controlled phase III study of ixazomib plus lenalidomide-dexamethasone in patients with relapsed/refractory multiple myeloma: China Continuation study. J Hematol Oncol. 2017 Jul 6;10(1):137.	Lenalidomide in all comparison arms
Iida S, Wakabayashi M, Tsukasaki K, et al. Bortezomib plus dexamethasone vs thalidomide plus dexamethasone for relapsed or refractory multiple myeloma. Cancer Sci. 2018 May;109(5):1552-1561.	Intervention/comparison outside our scope
Kropff M, Vogel M, Bisping G, et al Bortezomib and low-dose dexamethasone with or without continuous low-dose oral cyclophosphamide for primary refractory or relapsed multiple myeloma: a randomized phase III study. Ann Hematol. 2017 Nov;96(11):1857-1866.	Intervention/comparison outside our scope
Lonial S, Dimopoulos MA, Weisel K, et al. Extended 5-y follow-up (FU) of phase 3 ELOQUENT-2 study of elotuzumab+ lenalidomide/dexamethasone (ELd) vs Ld in relapsed/refractory multiple myeloma (RRMM). J Clin Oncol. 2018 May; 36 (15S): 8040.	Lenalidomide in all comparison arms
Mateos MV, Sonneveld P, Hungria VT, et al.. Efficacy and Safety of Daratumumab, Bortezomib, and Dexamethasone (D-Vd) Versus Bortezomib and Dexamethasone (Vd) in First Relapse Patients: Two-Year Update of Castor. Blood. 2018; 132 (S1): 3270	Intervention/comparison outside our scope
Montefusco V, Corso A, Galli M, et al. Bortezomib/cyclophosphamide/dexamethasone versus lenalidomide/cyclophosphamide/dexamethasone in multiple myeloma patients at first relapse: final results of a phase III study. Blood. 2017; 130 (S1): 836.	New evidence of no improvement in efficacy in the lenalidomide arm

Moreau P, Masszi T, Grzasko N, et al; TOURMALINE-MM1 Study Group. Oral Ixazomib, Lenalidomide, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2016 Apr 28;374(17):1621-34.	Lenalidomide in all comparison arms
Orlowski RZ, Moreau P, Ludwig H, et al. Carfilzomib and dexamethasone (Kd56) vs bortezomib and dexamethasone (Vd) in relapsed or refractory multiple myeloma (RRMM): Updated overall survival (OS), safety, and subgroup analysis of ENDEAVOR. J Clin Oncol. 2018 May; 36 (15S): 8032.	Intervention/comparison outside our scope
Richez V, Gruchet C, Guidez S, et al. Carfilzomib weekly 20/56 mg/m(2) , lenalidomide and dexamethasone for early relapsed refractory multiple myeloma. Am J Hematol. 2019 Jan;94(1):E17-E20.	Study design does not meet our criteria for assessing efficacy
Richardson P, Rocafiguera AO, Beksac M. Optimism: phase 3 trial of pomalidomide, bortezomib, and low-dose dexamethasone versus bortezomib and low-dose dexamethasone in lenalidomide-exposed patients with relapsed/refractory multiple myeloma. Proceedings from the European Hematology Association. 2018 Jun;14:17.	Intervention/comparison outside our scope
San-Miguel JF, Hungria VT, Yoon SS, et al. Overall survival of patients with relapsed multiple myeloma treated with panobinostat or placebo plus bortezomib and dexamethasone (the PANORAMA 1 trial): a randomised, placebo-controlled, phase 3 trial. Lancet Haematol. 2016 Nov;3(11):e506-e515.	Intervention/comparison outside our scope
Siegel DS, Dimopoulos MA, Ludwig H, et al. Improvement in Overall Survival With Carfilzomib, Lenalidomide, and Dexamethasone in Patients With Relapsed or Refractory Multiple Myeloma. J Clin Oncol. 2018 Mar 10;36(8):728-734.	Lenalidomide in all comparison arms
Spencer A, Lentzsch S, Weisel K, et al. Daratumumab plus bortezomib and dexamethasone versus bortezomib and dexamethasone in relapsed or refractory multiple myeloma: updated analysis of CASTOR. Haematologica. 2018 Dec;103(12):2079-2087.	Intervention/comparison outside our scope
Terpos E, Gobbi M, Potamianou A, et al. Retreatment and prolonged therapy with subcutaneous bortezomib in patients with relapsed multiple myeloma: A randomized, controlled, phase III study. Eur J Haematol. 2018 Jan;100(1):10-19.	Intervention/comparison outside our scope
Van Sanden S, Perualila N, Diels J, et al. Adjustment for the impact of subsequent therapies not available in UK on overall survival (OS) in CASTOR trial: A subgroup analysis in second-line (2L) patients. Value Health. 2018 Oct 1;21:S400.	Intervention/comparison outside our scope
Weisel KC, Siegel D, San Miguel JF, et al. Overall survival of patients with relapsed multiple myeloma treated with carfilzomib and dexamethasone versus bortezomib and dexamethasone according to prior line of therapy and previous exposure to bortezomib: secondary analysis of the phase 3 endeavor study. Blood. 2017; 130 (S1): 1850	Intervention/comparison outside our scope
Andorsky D, Coleman M, Yacoub A, et al. Response rate to lenalidomide plus rituximab (R2) as independent of number of prior lines of therapy: Interim analysis of initial phase of MAGNIFY phase IIIb study of R2 followed by maintenance in relapsed/refractory indolent NHL. J Clin Oncol. 2018 May; 36 (15S): 7516.	Abstract – limited information on study design

Andorsky DJ, Yacoub A, Melear JM, et al. Phase IIIb randomized study of lenalidomide plus rituximab (R2) followed by maintenance in relapsed/refractory NHL: Analysis of patients with double-refractory or early relapsed follicular lymphoma (FL). J Clin Oncol. 2017 May; 35 (15S): 7502.	Abstract – limited information on study design
Cadenas FL, Lumbreras E, Xicoy B, et al. Phase 3 Study of Lenalidomide (LEN) Vs Placebo in Non-Transfusion Dependent (TD) Low Risk Del (5q) MDS Patients with Del (5q)—Preliminary Blinded Analysis of the European Sintra-REV Trial. Blood. 2018; 132 (S1): 468.	Abstract – limited information on study design
Leonard JP, Trneny M, Izutsu K, et al; AUGMENT Trial Investigators. AUGMENT: A Phase III Study of Lenalidomide Plus Rituximab Versus Placebo Plus Rituximab in Relapsed or Refractory Indolent Lymphoma. J Clin Oncol. 2019 May 10;37(14):1188-1199.	Study publication date outside scope timeline
Lopez Cadenas F, Xicoy B, Bargay J, et al. Preliminary analysis of efficacy and safety of SINTRA-REV clinical trial, lenalidomide vs placebo phase 3 study in low/int-1 MDS patients with del (5Q) and transfusion independency. Haematologica. 2017 June; 102: 484-485.	Previously known information about lenalidomide related to safety

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

Appendix J. ICER Responses to Manufacturer Comments

General Evidence Response

Many manufacturer comments focused on the evaluation and interpretation of evidence within the UPI assessment. 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 assessment. 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 three-year period, there will virtually always be new published information about widely used medications. However, for ICER to consider such information as potentially providing support for a price increase there must be some question that was evaluated such that there is an answer that could be counted, a priori, as **not** supporting a price increase had the results come out differently. For instance, if the hazard ratio for survival with a therapy has been shown to be 0.72 with four years of follow-up and at eight years of follow-up the 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 in order to support a price increase. In the example above, if it was assumed that the HR for survival would persist over time, and at eight years of follow-up the hazard ratio was again 0.75, this would not be considered support. In contrast, had there been serious reasons for concern that the effect of therapy decreased substantially over time, a hazard ratio of 0.75 at eight years could provide support.
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 assessment.
    b. High-quality RWE can be particularly valuable in assessing the effectiveness of therapies and issues around adherence.
3. Quality of observational evidence
    a. As noted in the UPI Protocol, other than for assessing rare adverse events, ICER only reviewed observational studies as part of the UPI assessment process that were high quality and comparative.

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.
    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. Economic analyses based on modeling of prior evidence do not count as new clinical evidence under the UPI Protocol.

#	Comment	Response/Integration
	AbbVie Inc.	
1.	"ICER stated in Section 4 (Overview of Review Process) of the UPI Assessment protocol that it will perform independent systematic review of evidence from "randomized trials and high quality comparative observational studies, along with studies reporting patient-reported outcomes and other real-world data." ICER further stated it would consider evidence of moderate or high quality and rate the degree of additional net health benefit demonstrated by that evidence. Finally, per ICER, only drugs with evidence of substantial improvement in net health benefit will be categorized as having a "price increase with new clinical evidence." To assist ICER with this systematic review, AbbVie provided more than 200 scientific publications that support the value of HUMIRA and its safety and clinical effectiveness. Despite these being peer-reviewed publications – many of which have been presented at major medical congresses around the world – ICER determined that none of the evidence fully met the review process criteria. It is AbbVie's position that in rejecting all of AbbVie's submitted research from consideration, ICER has excluded high-quality evidence of added net health benefit of HUMIRA that would be appropriate to consider under the UPI assessment protocol. ICER cannot conduct a thorough analysis without considering the totality of the evidence that demonstrates value of a product to patients, clinicians, and payers."	See General Evidence Reponses 1a, 1b, and 3b.
2.	"*Keystone, EC et al. Achieving Comprehensive Disease Control in Patients with Early and Established Rheumatoid Arthritis Treated with Adalimumab Plus Methotrexate Versus Methotrexate Alone. RMD Open 2017;3: e000445. doi:10.1136/rmdopen-2017-000445*"	This is a post-hoc analysis of trials that were published in 2013 or earlier. This is not new clinical evidence.

#	Comment	Response/Integration
3.	"*Kavanaugh, A et al. Testing Treat-to-Target Outcomes with Initial Methotrexate Monotherapy Compared with Initial Tumor Necrosis Factor Inhibitor (Adalimumab) Plus Methotrexate in Early Rheumatoid Arthritis. Ann Rheum Dis. 2018 Feb;77(2):289-292. doi: 10.1136/annrheumdis-2017-211871*"	This trial does not provide new clinical evidence on the clinical effectiveness of adalimumab. Instead, it compares two adalimumab treatment strategies in patients with early rheumatoid arthritis (i.e., starting with methotrexate and adding adalimumab after 26 weeks versus combining adalimumab with methotrexate on day one).
4.	"*Emery, P et al. Effect of Adalimumab on the Work-Related Outcomes Scores in Patients with Early Rheumatoid Arthritis Receiving Methotrexate. Rheumatology, 2016, Vol.55(8), p.1458l*"	This is a post-hoc analysis of trials that were published in 2013 or earlier. This is not new clinical evidence.
5.	"*Travis, S et al. Effect of Adalimumab on clinical efficacy and Health-Related Setting: Results from Inspirada. J Crohns Colitis. 2017 Oct 27;11(11):1317-1325. doi: 10.1093/ecco-jcc/jjx093*"	This is a single-arm trial. As noted in the UPI Protocol, other than assessing rare adverse events, we considered evidence from only randomized controlled trials and high-quality comparative observational studies.
6.	"*Menter, A et al. Long-term safety and effectiveness of adalimumab for moderate to severe psoriasis: results from 7-year interim analysis of the esprit registry. Dermatology and Therapy, September 2017, Volume 7, Issue 3, pp 365–381.*"	This trial provides previously known safety information on adalimumab. Please also see General Evidence Response 1b.
7.	"*Strober, B et al. Systematic review of the real-world evidence of adalimumab safety in psoriasis registries. J Eur Acad Dermatol Venereol. 2018 Dec;32(12):2126-2133. doi: 10.1111/jdv.15203*"	This trial provides previously known safety information on adalimumab. Please also see General Evidence Response 1b.
8.	"*Nash, P et al. Randomized Crossover Comparison of Injection Site Pain with 40 mg/0.4 or 0.8 mL Formulations of Adalimumab in Patients with Rheumatoid Arthritis Rheumatol Ther. 2016 Dec; 3(2): 257–270.*"	This trial does not provide new clinical evidence on the clinical effectiveness of adalimumab. It is specifically focused on comparing the injection pain associated with the use of two different formulations of adalimumab.
9.	"Examples of important and high-quality evidence that were submitted coming from registries include: • *Loftus, EV et al. Adalimumab Effectiveness Up to Six Years in Adalimumab-naïve Patients with Crohn's Disease: Results of the PYRAMID*	Both trials (Loftus et al. and Pappas et al.) are non-comparative analyses of registry data that showed no new information on adalimumab related to efficacy or safety. As noted in the UPI Protocol, other than assessing rare adverse

#	Comment	Response/Integration
	Registry Inflammatory Bowel Diseases, izz008, doi.org/10.1093/ibd/izz008. • *Pappas, DA et al. Long-Term Effectiveness of Adalimumab in Patients with Rheumatoid Arthritis: An Observational Analysis from the CORRONA Rheumatoid Arthritis Registry. Rheumatol Ther, 2017 ISSN: 2198-6576, 2198-6584.*"	events, we considered evidence from only randomized controlled trials and high-quality comparative observational studies. Please also see General Evidence Response 1b.
10.	"Patient support program: *Brixner, D et al. Patient Support Program Increased Medication Adherence with Lower Total Health Care Costs Despite Increased Drug Spending J Manag Care Spec Pharm, 2019 May. doi.org/10.18553/jmcp.2019.18443"*	This trial does not provide new clinical evidence on the clinical effectiveness of adalimumab. It is specifically focused on the evaluation of a patient support program.
	Amgen Inc.	
1.	"Based on actual data, Neulasta's net price change for the period evaluated is in line with inflation. Amgen understands that the cost of prescription drugs is a concern for many people, and we are committed to the responsible pricing of our innovative medicines. For 2019, the projected weighted average list price increase across Amgen's entire US portfolio of products is less than 3%, aligned with overall inflation and key pricing indices. For many Amgen medicines, there are no price increases. Amgen expects a single digit decline in the net price across our portfolio of all products in 2019 due to rebates and discounts negotiated with payers, providers, and others in the drug distribution chain to ensure patients continue to have access to our medicines. The actual net price change for Neulasta during ICER's analysis timeframe (Q4 2016 to Q4 2018) was in line with the general rate of inflation (2.2%), and was well below the rate of medical CPI. This means that the average price of other medical goods and services increased considerably faster than Neulasta's net price during the short period of time of the analysis.	Thank you for this information.

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	Amgen has publicly acknowledged that Neulasta's net selling price actually decreased by 1% in 2018 and is expected "to decline by mid-single digits in 2019" (See Appendix). For many Amgen medicines, there have been no price increases, with net prices for several other Amgen products declining. This situation is echoed in recent Express Scripts data, one of the nation's largest Pharmacy Benefits Managers, which revealed spending on medicines in commercial plans grew just 0.4% in 2018 net of rebates and discounts, the lowest in 25 years."	
2.	"The published literature and patient experiences represent real world experience, not subject to the limitations of randomized clinical trial design. Neulasta's evidence base specific from 2016 to 2018 (ICER's evaluation timeframe) included 31 abstracts and 80 peer-reviewed publications of which our initial data submission highlighted 12 studies. While ICER's preliminary assessment states that these studies are outside or irrelevant to the scope of their pricing assessment, these studies evaluated real-world outcomes that patients have identified as highly relevant, including improvements in quality of life and reductions in travel time. ICER states that all of Amgen's references submitted for Neulasta were excluded as none of the studies provided were randomized trials, yet many global regulatory authorities, including the US Food and Drug Administration consider RWE not only to improve treatment outcomes and support value, but also to support regulatory decision-making. FDA's draft guidance for industry is expected by year 2021, followed by final guidance in 2023. However, the FDA is already considering application of RWE in the approval of new indications. RWE was recently used by the FDA to support the approval of Ibrance in the treatment	Please see General Evidence Responses 1a, 1b, and 2a.

#	Comment	Response/Integration
	of male breast cancer. We appreciate that ICER is evaluating the best approach to incorporate RWE into its value framework, and we encourage ICER to also incorporate RWE into its UPI Assessments, especially for mature products where RWE is more relevant than randomized controlled trial data."	
3.	"Neulasta's actual net price change from Q4 2016 to Q4 2018 was in line with inflation, and the value of Neulasta is supported with RWE that documents improvements in areas of particular importance to cancer patients, their caregivers, and providers. For many Amgen medicines, there have been no price increases, with net prices for several other Amgen products, such as Neulasta, declining. In evaluating the value evidence of Neulasta, it is important to include not only clinical data but other determinants of patient value represented by real world evidence."	Please see General Evidence Responses 2a and 2b.
	Biogen Inc.	
1.	"Seventeen of the studies submitted were comparative effectiveness studies that consistently demonstrate that Tecfidera has superior clinical outcomes compared to glatiramer acetate, teriflunomide, and interferons and similar outcomes to fingolimod. Results from various other prospective, observational studies submitted demonstrate Tecfidera's significant impact on quality of life and the ability to work for patients with MS as well as healthcare resource utilization. Biogen respectfully disagrees with the exclusion for these studies as they provide important new clinical information on Tecfidera not previously published. While observational studies do not always merit a similar quality grade to RCTs, it is disappointing that this research has been excluded in ICER's	We provided the reasons for excluding all 17 studies in Appendix Table H1 of our report. As noted in our UPI Protocol, we considered only new clinical evidence made available over the prior 36 months on benefits and harms (within indication[s] that are responsible for approximately 10% or more of the drug's utilization) that was generated from randomized controlled trials or high-quality comparative observational studies. Please see the response to the comment below.

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	assessment as it can inform clinical care. For instance, excluding these 17 comparative effectiveness studies dismisses a large volume of previously unpublished, peer-reviewed, scientific evidence that shows consistently that Tecfidera has superior outcomes as compared to teriflunomide, glatiramer acetate, and interferons and similar outcomes as compared to fingolimod. ICER's reliance on the GRADE method for evaluation of evidence is inconsistent with the evolution of key stakeholders' sources of evidence and increasing emphasis on use of real-world comparative effectiveness research. Furthermore, payers, clinicians, and regulators increasingly look to well-conducted (e.g., propensity score matching to address selection bias and confounding) observational studies to address existing evidence gaps, such as efficacy in populations not previously studied in RCTs due to rigid inclusion/exclusion criteria. Real-world comparative effectiveness research is also more likely to be considered when head-to-head RCTs are not feasible or require a large sample size or significant follow-up time. Therefore, ICER should carefully consider methodological approaches taken to control for confounding and selection biases in observational studies rather than excluding all observational data as low-quality evidence."	
2.	"The research by Braune and colleagues was a comparative effectiveness study conducted in the German setting, and it is the only reference included in the assessment as a high-quality observational study. However, there are several excluded references that not only utilize similar methodologies (e.g., propensity score matching) and efficacy measures (e.g., time to first relapse) but also provide additional evidence on clinical	As stated in the report, these studies were excluded for the following reasons: Reference 4 (Buron 2019): This reference was not considered because it was published outside the timeframe of our review. Reference 6 (Hersh 2016): This study provides previously known information (dimethyl fumarate

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	parameters such as T2, gadolinium enhancing lesions, and NEDA-3. Additionally, they include various patient populations not studied by Braune, such as those in the US setting, treatment naïve patients, and those switching from another MS disease modifying therapy. *Biogen strongly recommends that ICER include the studies noted above in the assessment as they utilize similar methods as Braune et al. and provide additional evidence across patient populations and efficacy parameters."*	did not have improved effectiveness compared to fingolimod). And in fact, dimethyl fumarate was worse in some outcomes compared to fingolimod (e.g., earlier time to discontinuation and earlier relapse). Reference 8 (Spelman 2016): This study provides previously known information (dimethyl fumarate did not have improved effectiveness compared to fingolimod). Reference 9 (Vollmer 2018): This study provides previously known information (dimethyl fumarate did not have improved effectiveness compared to fingolimod). Reference 15 (Prosperini 2018): This study provides previously known information (dimethyl fumarate did not have improved effectiveness compared to fingolimod).
Eli Lilly and Company		
1.	"Lilly appreciates the opportunity to respond to ICER's preliminary assessment. As noted in previous comment letters from various pharmaceutical companies, there are several outstanding questions regarding the methodologies and data used in developing this report. We encourage ICER to continue to improve the transparency of its methods and analyses to enable the reproducibility of its assessments. It is difficult to discern (even using the PRISMA flow chart and GRADE methodology) which publications were reviewed and how such studies were ultimately considered/classified. Additionally, the current methodology utilizes too narrow of inclusion and exclusion criteria for the systematic literature review which creates a limited subsection of the existing evidence for a given medicine. This abbreviated view does not	Manufacturers had (and most took) the opportunity to submit to ICER relevant studies and trials, and then to raise specific concerns about ICER's decisions on the quality or interpretations of the evidence.

#	Comment	Response/Integration
	take into account the totality of evidence for a medicine, including other potential factors that influence price changes."	
2.	"Finally, in the case of Cialis, the patent has expired, and low-cost generic manufacturers can and do replicate the science. As a result, this invention is highly accessible and at a very low cost."	Thank you for this information.
	Genentech Inc.	
1.	"We believe that ICER's approach to their UPI assessment is significantly flawed. Genentech has previously provided public comments and suggestions for improving the UPI methodology. Specifically, ICER's scope and methodology disconnects the value and price of Rituxan by explicitly excluding meaningful, high quality, and peer-reviewed evidence that support its clinical, economic, and humanistic value. ICER's arbitrary and narrow selection of evidence stands in direct contradiction to the judgements of the scientific community that has deemed the evidence worthy of publication after a peer review process."	Please see General Evidence Responses 1a and 1b.
2.	"ICER should include publications that demonstrate the economic and humanistic benefits associated with Rituxan in the UPI assessment. Economic and patient-reported outcomes should be considered relevant to the scope of the UPI assessment and included as new evidence in support of Rituxan. Economic and patient-reported outcomes continue to inform payer, provider, and patient health care decisions, and demonstrate the additional value of an intervention. Although the UPI framework specifically excludes cost-effectiveness models, analyses of economic outcomes over time should be included to holistically determine the benefit an intervention provides."	Please see General Evidence Responses 1a, 1b, 2a, 4a, and 4b.

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3.	"Improvements in health-related quality of life (HRQoL) over time in patients with advanced FL should be included in the UPI assessment. The Watch and Wait trial should be included in the review because improvements in HRQoL scores for patients treated with Rituxan maintenance, compared to watchful waiting, had not been previously reported. The patients in the Rituxan maintenance arm were significantly more likely to feel in control of their situation than those patients in the watchful waiting arm. When compared to patients in the Rituxan maintenance arm, those in the watchful waiting arm were significantly more likely to avoid learning or thinking about their illness and to have unpleasant connotations associated with their clinic visits. These patient-reported outcomes were not previously known information about Rituxan maintenance therapy and should be incorporated into the UPI assessment as new clinical evidence."	We do not believe that a study demonstrating that patients have less anxiety when they are treated rather than delaying treatment justifies increasing the price of that treatment.
4.	"Evidence demonstrating the substantial clinical benefit of Rituxan in rare diseases with high unmet need should be included in the UPI assessment as new clinical evidence. The clinical evidence supporting Rituxan's use in pemphigus vulgaris (PV), granulomatosis with polyangiitis (GPA), and microscopic polyangiitis (MPA) should be included as new clinical evidence despite failing to meet ICER's inclusion criteria of indications assuming 10% of overall sales revenue. Rituxan has changed the treatment landscape of these rare diseases, and ICER's criteria ignores the body of evidence generated for rare diseases. Rituxan has demonstrated significant net health benefit in these serious and potentially life-threatening conditions."	We have no disagreement that the introduction of rituximab has been an extremely important development in medical care over recent years. We do not believe that widened use to new populations justifies price increases that affect costs for the large populations who already had diseases for which the drug is indicated.

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5.	"ICER's exclusion of recently published evidence they deem to be "previously known information" discounts new and important clinical evidence, including RWE, long-term follow-up to clinical trials, and studies of novel therapies with Rituxan as a "backbone." Real-world studies should be considered as new clinical evidence and included in the UPI assessment because they complement clinical trial information by evaluating interventions in a more generalizable population and context, better informing health care decisions. Increasingly, clinicians and payers leverage RWE to better understand an intervention's long-term outcomes in patient populations not studied in clinical trials. With over 20 years of post-marketing experience, the evidence base for Rituxan is broad and consists of both clinical trials and RWE. By employing narrow inclusion criteria and excluding important RWE, the UPI assessment is limited and does not reflect the totality of evidence for Rituxan."	Please see General Evidence Responses 1a, 1b, 2a, and 2b.
6.	"Overall survival (OS) benefits in first-line FL with Rituxan maintenance should be included in the UPI assessment. While the Rituxan prescribing label discusses improvements in progression-free survival (PFS) in patients receiving Rituxan maintenance therapy, controversy remains around whether Rituxan maintenance therapy following chemoimmunotherapy in first-line treatment of FL improves OS. A retrospective analysis of the Veterans Health Administration's electronic health record was the first to examine the association of Rituxan maintenance with OS in a real-world cohort. Compared to patients who were not on maintenance, patients receiving Rituxan maintenance were associated with	We have reevaluated this retrospective analysis of the Veterans Health Administration's electronic health record presented in the form of a conference abstract. We still conclude that this falls under previously known information about rituximab. As cited in the background section of the conference abstract, an individual patient data (IPD) meta-analysis of seven randomized controlled trials published in 2014 or earlier showed that maintenance rituximab improved overall survival. In fact, the authors of the meta-analysis concluded that *"maintenance rituximab improves overall survival consistently in all patients, regardless of patient and disease characteristics when compared with observation,"* based on the IPD analyses of the randomized

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	improved OS, offering important information that was not included in the original Rituxan label."	controlled trials published in 2014 or earlier. As such, we do not consider this conference abstract new clinical evidence to be included.
7.	"The UPI assessment should include analyses characterizing the real-world safety profile of Rituxan in autoimmune settings. Although progressive multifocal leukoencephalopathy (PML) in patients receiving Rituxan is well-described in the oncology setting, being added as a black box warning in 2007, less is known in the autoimmune setting. An analysis of post-marketing spontaneous reports and the clinical trial programs for RA and GPA/MPA, observed an estimated rate of PML cases of 2.56 per 100,000 patients with RA and <1 per 10,000 patients with GPA/MPA. This study further characterizes the safety profile of Rituxan in patients with severe autoimmune disorders and provides previously unpublished information to support the use of Rituxan."	Please see General Evidence Responses 1a and 1b.
8.	"Comparative effectiveness of Rituxan versus other targeted immune modulators should be included in the UPI assessment. Comparative real-world studies inform healthcare decision makers about the relative benefit and risk of Rituxan relative to other therapies. For example, in a weighted cohort analysis of three registries, Rituxan had longer drug retention and improved disease activity compared with abatacept. In a separate registry analysis, the risk of serious infection was similar in patients using Rituxan or a second tumor necrosis factor inhibitor (TNFi) following initial TNFi failure. By assessing the benefit and risk of Rituxan relative to other therapies, these studies contribute to the body of evidence beyond what was previously known to better inform health care decision making."	Please see General Evidence Responses 1a and 1b.

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9.	"Long-term follow up of clinical studies reduce uncertainty about and enhance the confidence in the net health benefit that Rituxan provides to patients. Advanced FL remains an indolent incurable lymphoma; therefore, the long-term benefits in this patient population should be included in ICER's assessment. • The UPI assessment should include the effects of Rituxan maintenance observed over 10 years in first-line patients with FL. While the PRIMA study established that two years of Rituxan maintenance after first-line therapy in patients with FL significantly improved PFS, a recent publication reports the final PFS, OS, and safety overview after nine years. The median PFS was 10.5 years in the Rituxan maintenance arm compared with 4.1 years in the observation arm. The 10-year OS estimates were approximately 80% in both study arms, and there was no statistically significant difference in OS between patients randomized to Rituxan maintenance or observation. No new safety signals were observed."	Please see General Evidence Responses 1a and 1b.
10.	"In addition, several novel therapies have been studied in combination with Rituxan, demonstrating its importance as the anti-CD20 backbone in an evolving treatment landscape. Given Rituxan was in both arms for the following trials, we believe this demonstrates Rituxan's status as standard of care in the hematology setting where appropriate. • Rituxan served as the backbone for the venetoclax and polatuzumab registrational trials, and this evidence should be included in the UPI assessment. The MURANO trial studied Rituxan plus the novel therapy venetoclax compared to bendamustine plus	Studies using rituximab in both arms do not provide new clinical evidence about the effectiveness of rituximab.

#	Comment	Response/Integration
	Rituxan in patients with relapsed or refractory CLL. Patients in the venetoclax plus Rituxan arm had a significantly higher PFS compared to those in the bendamustine plus Rituxan arm. In addition, polatuzumab was recently approved for relapsed or refractory DLBCL. The registrational trial for polatuzumab, GO29365, studied the effects of polatuzumab in combination with bendamustine and Rituxan."	
	Gilead Sciences Inc.	
1.	"Recent data from implementation projects demonstrate the remarkable impact of Truvada for pre-exposure prophylaxis (PrEP) in real-world settings. Real-world data are critical to understanding medicines' value to society, and we strongly believe that they should be considered when evaluating drug prices. This is particularly true for indications with the potential to significantly impact public health, such as PrEP. In the case of Truvada, these data provide new evidence of impact and value in diverse populations and settings. Recent research has also contributed to our understanding of the cost-effectiveness of Truvada for PrEP. Just last year, a new analysis calculated that the lifetime costs of HIV care are higher than previously estimated, indicating that Truvada for PrEP provides even greater cost savings by preventing HIV infections."	Please see General Evidence Responses 2a, 4a, and 4b.
2.	"While ICER's analysis does not address patient access, we believe it is important to recognize that the cost of Truvada for HIV treatment and prevention is not a significant obstacle to gaining access. In fact, a 2015 CDC analysis found that 1% of the estimated number of Americans at high risk for contracting HIV have an entirely unmet need for financial coverage for Truvada for PrEP."	Thank you for this information.

#	Comment	Response/Integration
3.	"Gilead is committed to ensuring that safe and effective HIV treatment and prevention medications are available to all who need them. Driven by this goal, Gilead continues to work to expand access to Truvada for PrEP. In 2018, we worked with the FDA to expand Truvada for PrEP's indication to include adolescents, who bear a high burden of new infections in the United States. We also maintain a package of patient assistance solutions for people who are prescribed Truvada, for both treatment and prevention. And we coordinate with community organizations to continually evaluate these programs on an ongoing basis."	Thank you for this information.

Appendix K. Manufacturer Comments

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

abbvie

September 9, 2019

Executive Summary

For the past 20 years, AbbVie has been a leader in the field of immunology through significant investments in research and development of new, innovative medicines and programs that meet the needs of patients and healthcare stakeholders around the world.

Since its FDA approval in 2002, HUMIRA has helped transform care for millions of patients who suffer from the significant and debilitating effects of immune-mediated diseases. AbbVie's continued investment in the body of research around HUMIRA, a complex biologic treatment, has resulted in a new therapeutic option for patients suffering from 10 different immune-mediated diseases in the U.S., including four orphan, or rare disease, conditions.

HUMIRA's long-term safety and efficacy are supported by more than 100 clinical trials including more than 33,000 patients. A combination of numerous clinical trials and real-world studies have established the value of HUMIRA in reducing the burden of immune-mediated, chronic inflammatory diseases for patients, including its potential to improve symptoms, quality of life, and work productivity, and its impact on rates of hospitalization and surgery in certain immune-mediated diseases.

AbbVie remains focused on discovering and developing transformative therapies that deliver compelling patient benefits, differentiated clinical performance and clear economic value to payers, while purposefully advancing the standard of care.

AbbVie's Position on ICER Unsupported Price Increase Assessment

AbbVie respectfully disagrees with the conclusions ICER reached regarding HUMIRA in its first Unsupported Price Increase (UPI) Assessment. ICER's analysis does not reflect the value and benefit that HUMIRA has demonstrated since its FDA approval in 2002. This perspective is based on certain limitations of ICER's methodology. Most notably:

- ICER's assessment does not adequately reflect the breadth of available high-quality evidence that demonstrates the added net health benefit of HUMIRA
- In limiting its UPI assessment to indications representing greater than 10 percent use, ICER eliminated data from smaller indications including rare conditions and pediatric populations that reflect innovation and improvement in net health benefit
- ICER's assessment does not consider AbbVie's continued investment and innovation in HUMIRA through the development of new patient-centric enhancements, patient registries, and patient support programs

AbbVie
1 North Waukegan Road
North Chicago, IL 60064

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ICER's Approach to Evidence Review

ICER stated in Section 4 (Overview of Review Process) of the UPI Assessment protocol that it will perform independent systematic review of evidence from "randomized trials and high quality comparative observational studies, along with studies reporting patient-reported outcomes and other real-world data." ICER further stated it would consider evidence of moderate or high quality and rate the degree of additional net health benefit demonstrated by that evidence. Finally, per ICER, only drugs with evidence of substantial improvement in net health benefit will be categorized as having a "price increase with new clinical evidence."

To assist ICER with this systematic review, AbbVie provided more than 200 scientific publications that support the value of HUMIRA and its safety and clinical effectiveness. Despite these being peer-reviewed publications – many of which have been presented at major medical congresses around the world – ICER determined that none of the evidence fully met the review process criteria. It is AbbVie's position that in rejecting all of AbbVie's submitted research from consideration, ICER has excluded high-quality evidence of added net health benefit of HUMIRA that would be appropriate to consider under the UPI assessment protocol. ICER cannot conduct a thorough analysis without considering the totality of the evidence that demonstrates value of a product to patients, clinicians and payers.

The following examples highlight some of the high-quality evidence of added net health benefit that AbbVie submitted to ICER and believes merit consideration under the UPI protocol:

- High-quality observational studies:
    - *Keystone, EC et al. Achieving Comprehensive Disease Control in Patients with Early and Established Rheumatoid Arthritis Treated with Adalimumab Plus Methotrexate Versus Methotrexate Alone. RMD Open 2017;3: e000445. doi:10.1136/rmdopen-2017-000445*
    - *Kavanaugh, A et al. Testing Treat-to-Target Outcomes with Initial Methotrexate Monotherapy Compared with Initial Tumor Necrosis Factor Inhibitor (Adalimumab) Plus Methotrexate in Early Rheumatoid Arthritis. Ann Rheum Dis. 2018 Feb;77(2):289-292. doi: 10.1136/annrheumdis-2017- 211871*

- Patient-reported Outcomes:
    - *Emery, P et al. Effect of Adalimumab on the Work-Related Outcomes Scores in Patients with Early Rheumatoid Arthritis Receiving Methotrexate. Rheumatology, 2016, Vol.55(8), p.1458*
    - *Travis, S et al. Effect of Adalimumab on clinical efficacy and Health-Related Setting: Results from Inspirada. J Crohns Colitis. 2017 Oct 27;11(11):1317-1325. doi: 10.1093/ecco-jcc/jjx093*

AbbVie
1 North Waukegan Road
North Chicago, IL 60064

- Real-World Evidence:
    - *Menter, A et al. Long-term safety and effectiveness of adalimumab for moderate to severe psoriasis: results from 7-year interim analysis of the esprit registry. Dermatology and Therapy, September 2017, Volume 7, Issue 3, pp 365–381.*
    - *Strober, B et al. Systematic review of the real-world evidence of adalimumab safety in psoriasis registries. J Eur Acad Dermatol Venereol. 2018 Dec;32(12):2126-2133. doi: 10.1111/jdv.15203.*

Importance of Research Regarding Rare Diseases and Pediatric Indications

Since approval in 2002, AbbVie has continued to invest in the discovery of HUMIRA to address important unmet medical needs. Since becoming an independent company in 2013, AbbVie has invested over $22 billion collectively in research and development. With respect to HUMIRA specifically, AbbVie's research has resulted in an important therapeutic option for patients suffering from 10 different diseases in the U.S., including rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), juvenile idiopathic arthritis (JIA), adult Crohn's disease (CD), pediatric Crohn's disease, ulcerative colitis (UC), plaque psoriasis (Ps), adult and adolescent hidradenitis suppurativa (HS), and adult and pediatric non-infectious uveitis (UV).

In limiting the assessment to only those indications representing greater than 10 percent of use, ICER excludes evaluation of clinical evidence for rare conditions and many pediatric indications. AbbVie disagrees with a methodology that discounts the investment in and value provided to pediatric patients and patients suffering from rare diseases, simply because such patients are fewer in number. Just as FDA incentivizes the development of evidence regarding the treatment of orphan diseases, ICER should acknowledge and consider in its assessment the value of investing in smaller, yet high burden, disease areas. As such, AbbVie believes that the ICER UPI protocol should also assign important value to AbbVie's investment and research regarding the safety and effectiveness of HUMIRA in pediatric populations, non-infectious uveitis and hidradenitis suppurativa.

Assessing the Value of HUMIRA -- Beyond the Medicine

AbbVie continually invests and innovates in HUMIRA through the development of new patient-centric enhancements, patient registries and patient support programs.

In 2018, several **enhancements** were made to HUMIRA with the introduction of HUMIRA Citrate-free. HUMIRA is administered via subcutaneous injection. In order to address one of the top most reported adverse events for Humira, as reported by the FDA Adverse Events Reporting System (FAERS) Public Dashboard and to provide patients with a more positive injection experience, citrate buffers were removed from the new presentation. In two clinical studies,

patients reported less pain immediately following injection with HUMIRA Citrate-free compared to the original form (pain, as measured by Visual Analog Scale, Mean 0.9 vs 4.2, p<0.001).

- *Nash, P et al. Randomized Crossover Comparison of Injection Site Pain with 40 mg/0.4 or 0.8 mL Formulations of Adalimumab in Patients with Rheumatoid Arthritis Rheumatol Ther. 2016 Dec; 3(2): 257–270.*

Other important enhancements include a thinner needle, one half of the volume to inject compared to the original form, and new dosing configurations that result in fewer injections during the starting doses for adult patients with Ps, CD, UC, non-infectious UV, and HS, pediatric patients with CD, and adolescent patients with HS. The HUMIRA Pen has also been enhanced to include a larger viewing window and painted numbers. Further, the black needle cover is no longer made with natural rubber latex. Pursuing development of this new presentation is part of AbbVie's ongoing commitment to advance and improve the patient experience with HUMIRA.

AbbVie **sponsored or provided support for over 20 registries** (e.g. *PYRAMID, CORRONA, ESPRIT, LEGACY)* including registries for nine immune-mediated diseases. On an annual basis, our financial support of these immunology registries exceeds $20 million. This investment helps the scientific community gain a better understanding of these chronic immune-mediated diseases, which may lead to improvements in the quality of care provided to the millions of patients afflicted by these immune-mediated diseases.

Examples of important and high-quality evidence that were submitted coming from registries include:

- *Loftus, EV et al. Adalimumab Effectiveness Up to Six Years in Adalimumab-naïve Patients with Crohn's Disease: Results of the PYRAMID Registry Inflammatory Bowel Diseases, izz008, doi.org/10.1093/ibd/izz008.*
- *Pappas, DA et al. Long-Term Effectiveness of Adalimumab in Patients with Rheumatoid Arthritis: An Observational Analysis from the CORRONA Rheumatoid Arthritis Registry. Rheumatol Ther, 2017 ISSN: 2198-6576, 2198-6584.*

AbbVie developed a **patient support program** (PSP) for HUMIRA, known as HUMIRA Complete in the U.S., which delivers an individualized product support experience through a combination of personal education and product support interactions, supported by an investment in digital solutions and sophisticated data management. A recent study evaluating the impact of HUMIRA Complete demonstrated that enrolled patients had all-cause medical costs that were significantly lower than patients who were not enrolled in a patient support program.

- *Brixner, D et al. Patient Support Program Increased Medication Adherence with Lower Total Health Care Costs Despite Increased Drug Spending J Manag Care Spec Pharm, 2019 May. doi.org/10.18553/jmcp.2019.18443.*

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In conclusion, a reliable and complete assessment of the value of HUMIRA should look holistically at AbbVie's investment in HUMIRA, from clinical studies to real-world data to product enhancements that support the patient experience. AbbVie remains focused on discovering and developing transformative therapies that deliver compelling patient benefits, safety vigilance, differentiated clinical performance and clear economic value, while purposefully advancing the standard of care. AbbVie hopes that the concerns it has raised about the methodology of the UPI Assessment will be considered and addressed to ensure reliable conclusions.

AbbVie
1 North Waukegan Road
North Chicago, IL 60064
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Amgen appreciates the opportunity to comment on ICER's Unsupported Price Increase (UPI) Preliminary Assessment of Neulasta®. We value the collaboration we have had with ICER on this effort and acknowledge the challenges in getting the analysis right. The complexity of the US pricing environment, often with a high degree of market competition, means that much of the information needed to conduct a complete analysis is not available to any single party, confidential to many stakeholders, and hence not easily analyzed. Therefore, there can be many results depending on the data available and assumptions made. When we conduct the analysis using ICER's methods with Amgen's aggregate net price data for Neulasta, we find that Neulasta's change in net price for the period evaluated is in line with various measured rates of inflation for the entire economy and health care specifically. In addition to providing this alternative perspective, we appreciate the opportunity to discuss the value Neulasta brings to patients as supported by real world evidence (RWE) which, unlike randomized trial data, is more readily available for products that are late in their lifecycles.

Based on actual data, Neulasta's net price change for the period evaluated is in line with inflation. Amgen understands that the cost of prescription drugs is a concern for many people, and we are committed to the responsible pricing of our innovative medicines. For 2019, the projected weighted average list price increase across Amgen's entire U.S. portfolio of products is less than 3.0 percent, aligned with overall inflation and key pricing indices.[1] For many Amgen medicines, there are no price increases. Amgen expects a single digit decline in the net price across our portfolio of all products in 2019 due to rebates and discounts negotiated with payers, providers and others in the drug distribution chain to ensure patients continue to have access to our medicines.[2] The actual net price change for Neulasta during ICER's analysis timeframe (Q4 2016 to Q4 2018)[3] was in line with the general rate of inflation (2.2%)[4], and was well below the rate of medical CPI.[5][6] This means that the average price of other medical goods and services increased considerably faster than Neulasta's net price during the short period of time of the analysis.

Amgen has publicly acknowledged that Neulasta's net selling price actually *decreased* by 1% in 2018 and is expected *"to decline by mid-single digits in 2019"*[7] *(See Appendix).* For many Amgen medicines, there have been no price increases, with net prices for several other Amgen products declining.[8] This situation is echoed in recent Express Scripts data, one of the nation's largest Pharmacy Benefits Managers, which revealed spending on medicines in commercial plans grew just 0.4% in 2018 net of rebates and discounts, the lowest in 25 years.[9] Amgen is also committed to delivering new solutions that tie payments to performance (*e.g.*, linking the price of our medicines to clinical outcomes). Along with other healthcare stakeholders, we recognize our role in making healthcare affordable so patients can access the medicines they need.

Amgen has continued to invest in innovation and real world evidence for Neulasta despite an increasingly crowded marketplace that continues to drive price erosion. Even in the face of impending competition, Amgen developed and launched the Neulasta® Onpro® on-body injector

(OBI) with no increase in unit price over the Neulasta Prefilled Syringe.[10] Since that time, market competition has intensified with the introduction of two long-acting G-CSF biosimilars, the first of which launched in 2018.[11] Neulasta Onpro will therefore, compete with a number of products, but will also continue to provide patients and physicians with an improved administration option. With this option, a healthcare provider may initiate administration with the OBI for Neulasta on the same day as the administration of cytotoxic chemotherapy, as long as the OBI for Neulasta delivers Neulasta no less than 24 hours after administration of cytotoxic chemotherapy. This can eliminate the need for a separate physician visit the day after chemotherapy to administer Neulasta. In the G-CSF market, prices are decreasing despite this recently introduced innovation available to patients. Customers now have more choices, continued innovation, *and* decreasing prices.

In 2019, the value of Neulasta and Neulasta Onpro (and indeed all G-CSFs in the market) continues to be supported through RWE, which is much more widely available and used by customers than randomized clinical trials for products late in their lifecycle. Despite fewer randomized trials for late-lifecycle products in general, there continued to be scientific results produced. There were 111 articles published for Neulasta between 2016 and 2018 that support its value using real-world evidence to document improvements in areas of particular importance to cancer patients, their caregivers and providers. The following is a brief summary of the ongoing research documenting uncontrolled and/or untreated febrile neutropenia and its consequences, as well as the benefits associated with appropriate, timely, and system-enhancing treatment made possible by continued innovation in the use of G-CSFs.

- **Patients with febrile neutropenia (FN) have a significantly higher risk of death than patients without FN, including overall, approximately 10% in-hospital mortality rates and significantly higher rates for patients with major comorbidities.**[12,13,14,15,16,17,18,19,20] Half of FN hospitalization episodes, outcomes, and costs are among cancer chemotherapy patients eligible for G-CSF prophylaxis; but who either did not receive G-CSF or received G-CSF inconsistent with guidelines.[21] FN is a serious and costly complication of myelosuppressive chemotherapy. According to the Center for Disease Control (CDC), over 80% of patients with FN in the US are hospitalized annually at a cost of $2.3 billion for adults and $439 million for children.[22,23,24]

- **Findings from real-world studies show that many patients do not receive G-CSFs or fare poorly from suboptimal administration of G-CSFs.** High-FN risk patients with greater travel burden are less likely to receive G-CSFs, and may be more likely to experience FN.[25] The odds of not receiving G-CSFs is 26–52% higher (depending on cancer type) for patients with a >80-min one-way travel time, compared to patients traveling <20-min. Adherence to G-CSFs is critical, since administration of pegfilgrastim at the first and every cycle thereafter reduces the risk of FN and FN-related hospitalizations by 94% and 93%, respectively.[26]

Further, suboptimal administration of pegfilgrastim on day 0 and days 4-5 after the first chemotherapy cycle is associated with significantly higher risk of FN than administration on days 1-3, with comparable results in subsequent cycles.[27]

- **More patients receive their full course of chemotherapy with Onpro.** Data show patients receive 19.4% more chemotherapy cycles when they used Onpro instead of PFS.[28] This is important because patients who receive their full course of chemotherapy are more likely to see tumor shrinkage and increasingly greater survival.

- **Neulasta Onpro reduces travel time, extra clinic visits and costs significantly for patients and providers compared to administration with pre-filled syringe.[29]** With the HCP-administered Neulasta Onpro, which is the same cost as the Neulasta PFS, patients do not need to return to their outpatient clinic for the injection the day after chemotherapy. Returning to the clinic on another day post chemotherapy poses a significant economic burden to patients and caregivers, in terms of travel time, transportation costs and additional co-pays.[30] In one study of 403,000 patients (1.713 million clinic visits) for prophylactic G-CSF injections, the average travel time was 62 minutes with time in clinic of 41 minutes. The total cost to patients represented $182 million annually or $450 per patient: these are costs that are reduced for patients who receive Neulasta Onpro.[31] This is in contrast to studies that show high FN-related hospitalization costs with clinic administered treatment in both commercially-insured and Medicare populations.[32,33,34]

- **Onpro has a high level of satisfaction with positive experiences from patients and staff administering it.[35]** The introduction of Onpro significantly reduces the need to schedule, or for patients to attend, return clinic visits for pegfilgrastim prophylaxis.[36] The benefits of Neulasta Onpro have been expressed clearly by patients,[37] who have mentioned that: *"I don't have to again be driven or drive to the infusion center… It takes me obviously a lot of time and hassle and headache to get there, having this and being able to have the infusion essentially done at home…reduces my stress level overall and I really believe that stress affects overall body and mind so I think that's a huge benefit."…"You saved three hours and you don't have to go sit in traffic, bother a friend, your body won't hurt as much, so that is where it really needs – it's not really how much time did you gain, it's about I don't have to go in there as much…*"

The published literature and patient experiences represent real world experience, not subject to the limitations of randomized clinical trial design. Neulasta's evidence base specific from 2016 to 2018 (ICER's evaluation timeframe) included 31 abstracts and 80 peer-reviewed publications of which our initial data submission highlighted 12 studies. While ICER's preliminary assessment states that these studies are outside or irrelevant to the scope of their pricing assessment, these studies evaluated real-

world outcomes that patients have identified as highly relevant, including improvements in quality of life and reductions in travel time. ICER states that all of Amgen's references submitted for Neulasta were excluded as none of the studies provided were randomized trials, yet many global regulatory authorities, including the U.S. Food and Drug Administration consider RWE not only to improve treatment outcomes and support value, but also to support regulatory decision-making.[38,39] FDA's draft guidance for industry is expected by year 2021, followed by final guidance in 2023.[40,41] However, the FDA is already considering application of RWE in the approval of new indications. RWE was recently used by the FDA to support the approval of Ibrance® in the treatment of male breast cancer.[42] We appreciate that ICER is evaluating the best approach to incorporate RWE into its value framework, and we encourage ICER to also incorporate RWE into its UPI Assessments, especially for mature products where RWE is more relevant than randomized controlled trial data.

Conclusion

Neulasta's actual net price change from Q4 2016 to Q4 2018 was in line with inflation, and the value of Neulasta is supported with RWE that documents improvements in areas of particular importance to cancer patients, their caregivers and providers**.** For many Amgen medicines, there have been no price increases, with net prices for several other Amgen products, such as Neulasta, declining.[43] In evaluating the value evidence of Neulasta, it is important to include not only clinical data but other determinants of patient value represented by real world evidence**.** Amgen is committed to making medicines affordable for patients and generating clinical and RWE to improve care.

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APPENDIX.

Amgen Public Comments Regarding Neulasta Price Changes

Q1 Earnings call, 4/30/19
Can you comment on the pricing trend for the rest of the year for Neulasta? **Murdo Gordon:** "I think overall we're pleased with how we're performing in the market despite 2 biosimilar competitors against Neulasta. In particular, we see good durability of our Onpro business, which is holding at around 60% share of the long-acting filgrastim franchise. We also continue to compete at an account by account level, and we defend, as you point out, significant volumes. What will drive further price erosion or potentially share erosion is the number of new competitive entrants and we're following that very closely going forward/"
1/2019, Q4 Earnings call
"We also recognize the potential challenges, including further generic competition to Sensipar, continued competitive dynamics for Enbrel, and competition against Aranesp and Neulasta. With regard to net selling prices, as referenced, overall net selling price decreased by 1% in 2018. We expect net selling prices to decline by mid-single digits in 2019."
7/26/18 Earnings
And then secondly, maybe I want to see if you have any comments on the potential entry of a Neulasta biosimilar in the second half. We saw a [line in] price at 33% discount on this price level. So what's the assumption on your second half run rate for Neulasta? And what's your defense strategy on Neulasta? **Anthony C. Hooper: "**So as regards to the Neulasta biosimilar, I mean, clearly, we've been competing in the marketplace with NEUPOGEN and biosimilars for a number of years now. The team stands ready and able to compete. We have a long legacy and history of reliable and consistency of quality supply. We have spent quite a bit of time converting the market to the Onpro device, which is a unique and innovative device, which is beneficial for both clinical practice and for patients themselves. And I think there's quite a difference in the marketplace between the list prices of these drugs and the ASP price."

September 17, 2019

RE: ICER's Unsupported Price Increase Assessment for dimethyl fumarate (Tecfidera)

Biogen appreciates the opportunity to comment on ICER's draft Unsupported Price Increase Assessment for Tecfidera. In this assessment, ICER aims to review new evidence for Tecfidera over a 36-month period on efficacy and economic outcomes to determine supported price increases over a 24-month period (December 31, 2016 – December 31, 2018).

Biogen Disagrees with ICER's Exclusion of 28 References Provided by Biogen

Biogen provided 29 references with new clinical information published over the 36-month period and no additional search for new evidence was conducted by ICER. Of the 29 references provided, ICER excludes 28 in their assessment.

Seventeen of the studies submitted were comparative effectiveness studies that consistently demonstrate that Tecfidera has superior clinical outcomes compared to glatiramer acetate, teriflunomide, and interferons and similar outcomes to fingolimod.[1-17] Results from various other prospective, observational studies submitted demonstrate Tecfidera's significant impact on quality of life and the ability to work for patients with MS as well as healthcare resource utilization.[12,18-21] Biogen respectfully disagrees with the exclusion for these studies as they provide important new clinical information on Tecfidera not previously published.

While observational studies do not always merit a similar quality grade to RCTs, it is disappointing that this research has been excluded in ICER's assessment as it can inform clinical care. For instance, excluding these 17 comparative effectiveness studies dismisses a large volume of previously unpublished, peer-reviewed, scientific evidence that shows consistently that Tecfidera has superior outcomes as compared to teriflunomide, glatiramer acetate, and interferons and similar outcomes as compared to fingolimod.

ICER's reliance on the GRADE method for evaluation of evidence is inconsistent with the evolution of key stakeholders' sources of evidence and increasing emphasis on use of real-world comparative effectiveness research. Furthermore, payers, clinicians, and regulators increasingly look to well-conducted (e.g., propensity score matching to address selection bias and confounding) observational studies to address existing evidence gaps, such as efficacy in populations not previously studied in RCTs due to rigid inclusion/exclusion criteria.[22-25] Real-world comparative effectiveness research is also more likely to be considered when head-to-head RCTs are not feasible or require a large sample size or significant follow-up time. Therefore, ICER should carefully consider methodological approaches taken to control for confounding and selection biases in observational studies rather than excluding all observational data as low-quality evidence.

Biogen strongly recommends that ICER re-evaluate the observational studies supporting the benefits of Tecfidera and consider approaches for assessing the value of previously unpublished real-world, observational research to clinical decision-making and patient care. It is important that reports such as these not devalue or reduce incentives for manufacturers to generate more evidence on the value of therapies to improve decision-making.

There is inconsistent application of methodologies in the inclusion and exclusion of evidence

The research by Braune and colleagues[3] was a comparative effectiveness study conducted in the German setting, and it is the only reference included in the assessment as a high-quality observational study. However, there are several excluded references[4,6-9,15] that not only utilize similar methodologies (e.g., propensity score matching) and efficacy measures (e.g., time to first relapse) but also provide additional evidence on clinical parameters such as T2, gadolinium enhancing lesions, and NEDA-3. Additionally, they include various patient populations not studied by Braune, such as those in the US setting, treatment naïve patients, and those switching from another MS disease modifying therapy.

Biogen strongly recommends that ICER include the studies noted above in the assessment as they utilize similar methods as Braune et al. and provide additional evidence across patient populations and efficacy parameters.

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September 9, 2019

Steven D. Pearson, MD, MSc, FRCP
President
Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109 USA

RE: Preliminary Report, ICER Unsupported Price Increase Project

Dear Dr. Pearson,

At Celgene, we have long adhered to our Principles for the Pricing of Innovative Medicines that guide our decisions about the pricing of the medicines we discover, develop, and distribute worldwide. These principles reflect our commitment to patient access, obligation to provide value for patients and the health system, drive for continuing innovation for the future, and the need for flexibility. It is with these principles in mind that we offer comments on the preliminary report for Revlimid as part of ICER's "Unsupported Price Increase Assessment" project.

After reviewing the preliminary findings, Celgene supports ICER's conclusion that Revlimid "had a price increase with new clinical evidence" during the period of analysis. While we appreciate ICER's conclusion, we wanted to highlight a few considerations as ICER prepares to release its first UPI report.

As a company committed to ongoing research and development, Celgene believes in the accretive power of clinical evidence and that every piece of evidence submitted – whether from studies that were randomized, single-arm, or outside the approved indication – advances the clinical community's understanding of both Revlimid and the diseases it treats. It is in this spirit that we submitted 57 references for ICER's consideration in its analysis. Celgene's ongoing investment in research has enhanced the value that Revlimid provides to patients, providers and the health system, and we believe these additional references contribute to the evidence of Revlimid's clinical and economic value.

We were pleased that ICER recognized the significance of the Holstein 2017 study which evaluated the efficacy and safety of lenalidomide versus placebo following autologous stem cell transplant in newly diagnosed myeloma patients. With a 91-months median follow-up, this study demonstrated overall survival improvement of 30 months, with a p-value of 0.0004.[1] As such, we believe this evidence shows substantial net benefit for myeloma patients.

A truly innovative therapy, Revlimid has transformed the treatment of patients with multiple myeloma, whether newly diagnosed, relapsed/refractory, or on maintenance therapy. Additional benefits of Revlimid continue to be demonstrated through Celgene's ongoing research and development, including expansions into other forms of cancer, like mantle cell lymphoma, previously treated follicular lymphoma and previously treated marginal zone lymphoma.

Furthermore, Revlimid continues to be the backbone of many of today's combination therapies, including several triplet regimens for multiple myeloma approved between 2016 and 2018 and the June 2019 approval of Revlimid in combination with daratumumab and dexamethasone for patients with newly diagnosed multiple myeloma (NDMM) who are not eligible for autologous stem cell transplant (ASCT).

Our continued investment – in Revlimid and beyond – is ultimately in the service of patients, and our goal – like yours – is to ensure that patients see value from our research and our products. We firmly believe that Revlimid's value is well-substantiated based on the merits of our clinical evidence, and is in accordance with our own definition and standards of value, as outlined in our annual Value and Innovation Framework Report.[2] Celgene appreciates the opportunity to provide comments on ICER's preliminary report as well as the comments that we previously submitted on the report's proposed methodology.

Sincerely,

Richard H. Bagger

Richard H. Bagger
Executive Vice President, Corporate Affairs and Market Access

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Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285
U.S.A.
www.lilly.com

September 9, 2019

RE: Lilly Response to ICER's UPI Preliminary Assessment of Cialis

The following comments on the preliminary assessment of Cialis are submitted on behalf of Eli Lilly and Company ("Lilly"). Lilly is one of the country's leading innovation-driven, research-based pharmaceutical and biotechnology corporations. Lilly is devoted to seeking answers for some of the world's most urgent medical needs through discovery and development of breakthrough medicines and technologies and through the health information we offer. Ultimately, the company's goal is to develop products that save and improve patients' lives.

Lilly appreciates the opportunity to respond to ICER's preliminary assessment. As noted in previous comment letters from various pharmaceutical companies, there are several outstanding questions regarding the methodologies and data used in developing this report. We encourage ICER to continue to improve the transparency of its methods and analyses to enable the reproducibility of its assessments. It is difficult to discern (even using the PRISMA flow chart and GRADE methodology) which publications were reviewed and how such studies were ultimately considered/classified. Additionally, the current methodology utilizes too narrow of inclusion and exclusion criteria for the systematic literature review which creates a limited subsection of the existing evidence for a given medicine. This abbreviated view does not take into account the totality of evidence for a medicine, including other potential factors that influence price changes.

Finally, in the case of Cialis, the patent has expired, and low-cost generic manufacturers can and do replicate the science. As a result, this invention is highly accessible and at a very low cost.

We appreciate the opportunity to provide comments for this assessment.

Sincerely,

Frank D. Cunningham
Senior Vice President, Managed Healthcare Services
Eli Lilly and Company
cunningham_frank_d@lilly.com

Genentech
A Member of the Roche Group

September 9, 2019

Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109

Dear ICER Review Panel:

Genentech appreciates the opportunity to respond to the inclusion of Rituxan (rituximab) in ICER's ongoing Unsupported Price Increase (UPI) assessment. As a leading biotechnology company, Genentech discovers, develops, and manufactures novel medicines to treat patients with serious and life-threatening conditions. Genentech is committed to innovation and this is demonstrated by our approximately $11 billion a year investment in Research & Development – more than any other healthcare company in the world.[1] In addition to the 40 medicines currently approved, we have more than 70 potential medicines in development.

Rituxan is an example of our commitment to scientific discovery and developing treatments for people with serious conditions who need new or better treatment options. Since its initial approval in 1997, Rituxan has become a significant innovation in the treatment of B-cell cancers and severe and rare autoimmune diseases.[2] It has been approved in 8 indications across 6 diseases, with the most recent approval occurring in June 2018. To date, over 6.4 million patients have been treated worldwide with Rituxan in FDA approved indications, and we are continuing our commitment to innovation through the conduct of 26 ongoing company-sponsored trials using Rituxan as an investigational drug.[3]

We believe that ICER's approach to their UPI assessment is significantly flawed. Genentech has previously provided public comments and suggestions for improving the UPI methodology. Specifically, ICER's scope and methodology disconnects the value and price of Rituxan by *explicitly excluding meaningful, high quality, and peer-reviewed evidence that support its clinical, economic, and humanistic value.* ICER's arbitrary and narrow selection of evidence stands in direct contradiction to the judgements of the scientific community that has deemed the evidence worthy of publication after a peer review process.

Per ICER's request, in June 2019 Genentech provided 143 references published over the past three years that support the value of Rituxan. All 143 references were rejected by ICER. To better align the UPI assessment with the totality of recent evidence that is available to support the value of a product, we encourage ICER to reconsider their decisions and highlight key recommendations below:

1. ICER should include publications that demonstrate the economic and humanistic benefits associated with Rituxan in the UPI assessment.
2. Evidence demonstrating the substantial clinical benefit of Rituxan in rare diseases with high unmet need should be included in the UPI assessment as new clinical evidence.
3. ICER's exclusion of recently published evidence they deem to be "previously known information" discounts new and important clinical evidence, including RWE, long-term follow-up to clinical trials, and studies of novel therapies with Rituxan as a "backbone."

1. ICER should include publications that demonstrate the economic and humanistic benefits associated with Rituxan in the UPI assessment.

Economic and patient-reported outcomes should be considered relevant to the scope of the UPI assessment and included as new evidence in support of Rituxan. Economic and patient-reported outcomes continue to inform payer, provider, and patient health care decisions, and demonstrate the additional value of an intervention. Although the UPI framework specifically excludes cost-effectiveness models, analyses of economic outcomes over time should be included to holistically determine the benefit an intervention provides.

- **The UPI assessment should include the economic benefits of life-years gained due to the addition of Rituxan to chemotherapy, which exceed the added cost of Rituxan treatment to the U.S. health care system.[4]** An epidemiologic simulation model of the addition of Rituxan to chemotherapy in diffuse large B-Cell lymphoma (DLBCL), follicular lymphoma (FL), and chronic lymphocytic leukemia (CLL) constitutes new information that extends beyond the highly selected trial populations presented in the prescribing label. Survival assumptions for the model were based on Surveillance, Epidemiology, and End Results (SEER) registry data, the authoritative source of cancer incidence and survival. SEER represents approximately 35% of cancer cases in the United States, and provides real-world insights into population health outcomes that cannot be gained from clinical trials alone. The model concludes the following:
    - The addition of Rituxan to chemotherapy is associated with 279,704 saved life-years in DLBCL, FL, and CLL patients diagnosed in the U.S. from 1998 to 2003.
    - The estimated value of these additional life years gained is $25.44 billion.
    - When adjusting for the direct medical cost of Rituxan ($8.92 billion), the incremental economic gain is $16.5 billion to the U.S. health care system.
- **Improvements in health-related quality of life (HRQoL) over time in patients with advanced FL should be included in the UPI assessment.[5]** The Watch and Wait trial should be included in the review because improvements in HRQoL scores for patients treated with Rituxan maintenance, compared to watchful waiting, had not been previously reported. The patients in the Rituxan maintenance arm were significantly more likely to feel in control of their situation than those patients in the watchful waiting arm. When compared to patients in the Rituxan maintenance arm, those in the watchful waiting arm were significantly more likely to avoid learning or thinking about their illness and to have unpleasant connotations associated with their clinic visits. These patient-reported outcomes were not previously known information about Rituxan maintenance therapy and should be incorporated into the UPI assessment as new clinical evidence.

2. Evidence demonstrating the substantial clinical benefit of Rituxan in rare diseases with high unmet need should be included in the UPI assessment as new clinical evidence.

The clinical evidence supporting Rituxan's use in pemphigus vulgaris (PV), granulomatosis with polyangiitis (GPA), and microscopic polyangiitis (MPA) should be included as new clinical evidence despite failing to meet ICER's inclusion criteria of indications assuming 10% of overall sales revenue. Rituxan has changed the treatment landscape of these rare diseases, and ICER's criteria ignores the body of evidence generated for rare diseases.

Rituxan has demonstrated significant net health benefit in these serious and potentially life-threatening conditions.

- Rituxan became the first and only therapy approved by the FDA for PV, a life-threatening autoimmune disease, and the first major advancement in the treatment of the disease in more than 60 years.[2, 6] In the RITUX3 study, after 24 months of Rituxan therapy 90% of patients with PV achieved complete remission compared with 34% in the prednisone group.[7] Patients treated with Rituxan also experienced less severe adverse events and had greater improvements in HRQoL.
- Rituxan in combination with glucocorticoids is the first and only FDA-approved medicine for adults with GPA and MPA.[2] GPA and MPA, two forms of vasculitis that negatively impact patients' HRQoL, have an estimated prevalence of 32 per million and 2.9 per million patients in the U.S., respectively.[8, 9] A recent label update provided a follow-up option for patients who had achieved disease control with induction treatment but may incur potential disease relapse.[2] The update was supported by the MAINRITSAN trial, which observed improvements in the occurrence of major relapses in patients receiving follow-up treatment, and the RaVeR observational study, which showed a consistent safety profile of Rituxan in rheumatoid arthritis (RA) and GPA and MPA.[10, 11]
- In recently published long-term follow-up at 60 months in the MAINRISTAN study, patients treated with Rituxan experienced significantly higher overall and relapse-free survival rates, compared to those receiving azathioprine.[12]

3. ICER's exclusion of recently published evidence they deem to be "previously known information" discounts new and important clinical evidence, including RWE, long-term follow-up to clinical trials, and studies of novel therapies with Rituxan as a "backbone."

<u>Real-World Evidence</u>

Real-world studies should be considered as new clinical evidence and included in the UPI assessment because they complement clinical trial information by evaluating interventions in a more generalizable population and context, better informing health care decisions. Increasingly, clinicians and payers leverage RWE to better understand an intervention's long-term outcomes in patient populations not studied in clinical trials.[13, 14] With over 20 years of post-marketing experience, the evidence base for Rituxan is broad and consists of both clinical trials and RWE. By employing narrow inclusion criteria and excluding important RWE, the UPI assessment is limited and does not reflect the totality of evidence for Rituxan.

- **Overall survival (OS) benefits in first-line FL with Rituxan maintenance should be included in the UPI assessment.** While the Rituxan prescribing label discusses improvements in progression-free survival (PFS) in patients receiving Rituxan maintenance therapy, controversy remains around whether Rituxan maintenance therapy following chemoimmunotherapy in first-line treatment of FL improves OS. A retrospective analysis of the Veterans Health Administration's electronic health record was the first to examine the association of Rituxan maintenance with OS in a real-world cohort.[15] Compared to patients who were not on maintenance, patients receiving Rituxan maintenance were associated with improved OS, offering important information that was not included in the original Rituxan label.

- **The UPI assessment should include analyses characterizing the real-world safety profile of Rituxan in autoimmune settings.** Although progressive multifocal leukoencephalopathy (PML) in patients receiving Rituxan is well-described in the oncology setting, being added as a black box warning in 2007, less is known in the autoimmune setting. An analysis of post-marketing spontaneous reports and the clinical trial programs for RA and GPA/MPA, observed an estimated rate of PML cases of 2.56 per 100,000 patients with RA and <1 per 10,000 patients with GPA/MPA.[16] This study further characterizes the safety profile of Rituxan in patients with severe autoimmune disorders and provides previously unpublished information to support the use of Rituxan.
- **Comparative effectiveness of Rituxan versus other targeted immune modulators should be included in the UPI assessment.** Comparative real-world studies inform healthcare decision makers about the relative benefit and risk of Rituxan relative to other therapies. For example, in a weighted cohort analysis of 3 registries, Rituxan had longer drug retention and improved disease activity compared with abatacept.[17, 18] In a separate registry analysis, the risk of serious infection was similar in patients using Rituxan or a second tumor necrosis factor inhibitor (TNFi) following initial TNFi failure.[19] By assessing the benefit and risk of Rituxan relative to other therapies, these studies contribute to the body of evidence beyond what was previously known to better inform health care decision making.

Long-term Follow up from Clinical Trials

Long-term follow up of clinical studies reduce uncertainty about and enhance the confidence in the net health benefit that Rituxan provides to patients. Advanced FL remains an indolent incurable lymphoma; therefore, the long-term benefits in this patient population should be included in ICER's assessment.

- **The UPI assessment should include the effects of Rituxan maintenance observed over 10 years in first-line patients with FL.** While the PRIMA study established that 2 years of Rituxan maintenance after first-line therapy in patients with FL significantly improved PFS, a recent publication reports the final PFS, OS, and safety overview after 9 years.[20, 21] The median PFS was 10.5 years in the Rituxan maintenance arm compared with 4.1 years in the observation arm. The 10-year OS estimates were approximately 80% in both study arms, and there was no statistically significant difference in OS between patients randomized to Rituxan maintenance or observation. No new safety signals were observed.

Evidence of Rituxan as an Important Combination Therapy

In addition, several novel therapies have been studied in combination with Rituxan, demonstrating its importance as the anti-CD20 backbone in an evolving treatment landscape. Given Rituxan was in both arms for the following trials, we believe this demonstrates Rituxan's status as standard of care in the hematology setting where appropriate.

- **Rituxan served as the backbone for the venetoclax and polatuzumab registrational trials, and this evidence should be included in the UPI assessment.** The MURANO trial studied Rituxan plus the novel therapy venetoclax compared to bendamustine plus Rituxan in patients with relapsed or refractory CLL.[21, 22] Patients in the venetoclax plus Rituxan arm had a significantly higher PFS compared to those in the bendamustine plus Rituxan arm. In addition, polatuzumab was recently approved for relapsed or refractory

DLBCL. The registrational trial for polatuzumab, GO29365, studied the effects of polatuzumab in combination with bendamustine and Rituxan.[23]

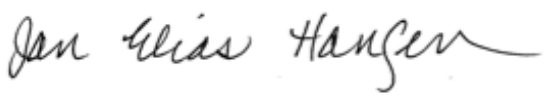
Conclusions

Rituxan has been an important innovation in many different diseases including CLL, DLBCL, FL, RA, PV, GPA, and MPA. The addition of Rituxan to chemotherapy is associated with 279,704 saved life-years in DLBCL, FL, and CLL patients diagnosed in the U.S. from 1998 to 2003 and an incremental economic gain of $16.5 billion to the U.S. health care system.

ICER's conclusion of unsupported price increase for Rituxan is flawed due to the intentional disconnect between value and price in the UPI framework as it currently exists. This has resulted in the exclusion of *meaningful, high quality, and peer-reviewed evidence that support the clinical, economic, and humanistic value of Rituxan*. We believe that an assessment of medicines should be value-based and comprehensively account for *all* available evidence to support the decision needs of patients, society, and the health care system. To that end, ICER's UPI evidence review should be expanded to include clinical, economic, and patient-reported outcomes from both trial-based and observational settings.

As a significant developer of biopharmaceutical innovations *and* generator of evidence that supports the value of our products throughout their lifecycles, we welcome the discussion on the value of Rituxan. We support the goals of policymakers to lower health system costs and to improve patient outcomes, their experience in the health care system, and the quality of care that they receive. To achieve this, stakeholders must work together to find sustainable, system-wide solutions that lower costs while protecting scientific innovation and access to breakthrough treatments.

Sincerely,



Jan Elias Hansen, PhD
Vice President, Evidence for Access
U.S. Medical Affairs, Genentech, Inc.

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October 2, 2019

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

DELIVERED ELECTRONICALLY

RE: Unsupported Price Increases Report

Dear Dr. Pearson:

On behalf of Gilead Sciences, we appreciate the opportunity to respond to ICER's preliminary assessment of Truvada® (emtricitabine/tenofovir disoproxil fumarate [FTC/TDF]). Truvada was approved following Gilead's investment of approximately six billion dollars in HIV research, $1.1 billion of which was devoted to Truvada. Today, Truvada and other Gilead HIV medications have contributed to nearly doubling the average life expectancy of people living with the disease. Additionally, Truvada is the first and only medicine currently available to help reduce the risk of HIV infection.

We believe that Truvada brings exceptional value to the U.S. healthcare system, due in part to its unique and important role in HIV prevention strategies. We respectfully disagree with ICER's decision to disregard data provided by Gilead demonstrating this value, and we provide further detail on our perspective below.

Real-world and cost-effectiveness data

Recent data from implementation projects demonstrate the remarkable impact of Truvada for pre-exposure prophylaxis (PrEP) in real-world settings.[1,2,3,4] Real-world data are critical to understanding medicines' value to society, and we strongly believe that they should be considered when evaluating drug prices. This is particularly true for indications with the potential to significantly impact public health, such as PrEP. In the case of Truvada, these data provide new evidence of impact and value in diverse populations and settings.

Recent research has also contributed to our understanding of the cost-effectiveness of Truvada for PrEP. Just last year, a new analysis calculated that the lifetime costs of HIV care are higher

than previously estimated,[5] indicating that Truvada for PrEP provides even greater cost savings by preventing HIV infections.

Price and access

While ICER's analysis does not address patient access, we believe it is important to recognize that the cost of Truvada for HIV treatment and prevention is not a significant obstacle to gaining access. In fact, a 2015 CDC analysis found that 1% of the estimated number of Americans at high risk for contracting HIV have an entirely unmet need for financial coverage for Truvada for PrEP.[6]

Gilead is committed to ensuring that safe and effective HIV treatment and prevention medications are available to all who need them. Driven by this goal, Gilead continues to work to expand access to Truvada for PrEP. In 2018, we worked with the FDA to expand Truvada for PrEP's indication to include adolescents, who bear a high burden of new infections in the United States. We also maintain a package of patient assistance solutions for people who are prescribed Truvada, for both treatment and prevention. And we coordinate with community organizations to continually evaluate these programs on an ongoing basis.

We thank ICER for the opportunity to share further information about the value of Truvada and welcome the opportunity for further discussion on this important topic.

Sincerely,

Bill Guyer
Senior Vice President and Head of Medical Affairs

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