2022

The Influence of US Drug Price Dynamics on Cost-Effectiveness Analyses of Biologics

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Abstract

Objective: To evaluate the influence of drug price dynamics in cost-effectiveness analyses (CEAs).

Methods: We evaluated scenarios involving typical US drug price increases during the exclusivity period and price decreases after the loss of exclusivity (LOE). Worked examples are presented using the Institute for Clinical and Economic Review's assessments of tezepelumab for the treatment of severe asthma and targeted immune modulators for rheumatoid arthritis.

Results: Tezepelumab case: Yearly 2% price increases during the period of exclusivity and a post-LOE price decrease of 25% yielded an incremental cost per QALY gained that increased over the base case from $430,300 to $444,600 (+3.2%). Yearly 2% price increases followed by a steeper post-LOE price reduction of 40% resulted in a cost per QALY gained of $401,400 (6.8% reduction versus the base case). Rheumatoid arthritis case: Incorporating post-LOE price reductions for etanercept (intervention) and adalimumab (comparator) ranging from 25% to 40% yielded an incremental cost per QALY of $121,000 and $122,300, respectively (<3% increase from the base case of $119,200/QALY). Including a 2% yearly price increase during the projected exclusivity periods of both intervention and comparator increased the cost per QALY gained by more than 60%.

Conclusion: In these two cases incorporating price dynamics in CEA had varied impacts on the cost-effectiveness ratio depending on the magnitude of pre-LOE price increase and post-LOE price decrease, and whether the LOE also affected the comparator. Yearly price increase magnitude during the period of exclusivity, among other factors, may counterbalance the effects of lower post-LOE intervention prices.

Highlights:

- Prior studies have revealed that accounting for a chronic drug's future loss of market exclusivity can improve the results of cost effectiveness analyses (CEA). However, no studies have examined the extent to which US price increases during the period of exclusivity may counterbalance this effect.
- Using frameworks from prior ICER assessments, we found that yearly price increases of 3% or higher in the years before a drug's loss of exclusivity (LOE) more than counterbalanced the effect of post-LOE price reductions, resulting in an overall increase in the cost per QALY gained.

Introduction

Prices change over a drug's life cycle, and this complicates the ability to conduct cost effectiveness analyses (CEA), particularly for chronic therapies that are assumed to be used over many years. Most CEAs do not account for price reductions that are likely to occur with the introduction of generic or biosimilar interventions or comparators,[1] or capture drug price increases that are likely to occur in the US during the exclusivity period.[2] While some CEA guidelines provide recommendations to account for future drug prices,[3,4] many do not.[1]

With other factors held constant, lower drug prices resulting from future loss of exclusivity (LOE) will improve a new drug's cost effectiveness. Conversely, an intervention's cost-effectiveness will be diminished when accounting for lower prices associated with the future LOE of a comparator drug. Drug price increases occurring during the period of exclusivity are

an additional dynamic that is particularly relevant for CEAs conducted for the US, where in recent years annual drug price increases have been higher than other nations.[5-7] It is challenging to forecast both the price increases that may occur during a drug's exclusivity period, and the magnitude of price reductions that might occur with a future generic or biosimilar. Nevertheless, these pricing dynamics may be important to capture in CEA, as they may influence whether a new therapy is considered to be cost-effective.

In this study we used two prior assessments conducted by the Institute for Clinical and Economic Review (ICER) to evaluate how drug price dynamics affect the cost effectiveness ratio. We assessed scenarios involving drug price increases during the period of exclusivity, and price decreases following the loss of exclusivity (LOE). Each scenario's impact on the incremental cost per quality-adjusted life year (QALY) gained was compared to the fixed-price base case from the original assessment. We sought to determine if modeling these potential price changes caused substantial changes in the CEA's results and interpretations, and obtain insights to inform the development of best practices.

Methods

We reviewed prior ICER assessments to identify CEAs involving chronic therapies that could potentially be used over a patient's lifetime. We sought examples that would provide a framework to assess the impact of incorporating price increases during the period of exclusivity and price decreases after LOE when a generic or biosimilar would become available. We also sought examples of diseases affecting adults, and involving prevalent (not rare) health conditions. ICER's 2021 assessment of tezepelumab for the treatment of severe asthma was

selected as one example of the use of a new chronic drug therapy over a lifetime horizon.[8] Data elements from the published ICER report on tezepelumab were used to recalculate the model's results for various price change scenarios. We redeveloped the cost cycles for tezepelumab in a separate Microsoft Excel®-based model using the same assumptions as the original assessment, which included a lifetime horizon, a patient age of 52 years at treatment initiation, and applying the same discount rate (3%) and age-specific probabilities of any cause mortality. Our redeveloped cost for tezepelumab matched the cost reported in the original report (within 0.1%). The impacts of future price dynamics were then determined using the revised tezepelumab cost estimates, and incremental cost effectiveness ratios were calculated using the comparator costs and QALYs reported in the in the original assessment. For a different example we sought an assessment involving the LOE of both an intervention drug and a comparator drug. We selected ICER's 2017 assessment of targeted immune modulators for rheumatoid arthritis, which evaluated etanercept in comparison with adalimumab. For this analysis, we had access to the original model.

Using the CEA frameworks of these two models, we examined pre-LOE price increases up to 4% yearly, and two post-LOE price decrease scenarios of differing magnitude. We selected a range of 0% to 4% rate of pre-LOE price increase because while yearly increases in US list prices for some drugs have exceeded 4%,[5,9] increases in US net prices (e.g. after rebates and other discounts) have been less dramatic and more varied.[10,11] Hernandez et al[2] examined trends in reported US list and net prices for 602 drugs from 2007 to 2018 and found that while list prices increased by an average of 9% per year, net prices grew by 4.5% yearly, albeit stabilizing after 2015. Thus, given recent trends of lower US net price growth rates, and recent US

legislation to penalize manufacturers for excessive drug price increases,[12] we have focused on the results of 2% yearly increases in net prices prior to LOE, while also providing the range of findings based on the 0% to 4% per year increase levels.

Jointly with pre-LOE price increases, we evaluated two post-LOE scenarios. LOE scenario A applied a 10% price decrease for the first year after LOE, and then applied a 25% decrease from the pre-LOE price in the following year and carried this price forward. LOE scenario B applied a larger 20% price reduction in the first year after LOE, followed by a 40% reduction in the following year, carried forward. While generics of traditional oral drugs may achieve even steeper price reductions over time and with more competition,[13] the two post-LOE scenarios we assessed are consistent with historical pricing for biosimilars.[10,14-15] For example, Herzuma™ was launched at a 10% discount to Herceptin™, the 2016 price of Inflectra™ was 19% less than Remicade™, and Nivestym's 2018 price was 37% less than Neupogen.[15]

For the first example assessing the effect of potential price dynamics on the CEA of tezepelumab for severe asthma, we assumed a 12-year period of exclusivity, as consistent with US protection for new biologics.[16] The post-LOE price reduction applied only to tezepelumab which was presumed to be added to usual care. For the rheumatoid arthritis example, we applied the expected LOE for adalimumab (comparator) in 2023[17] and etanercept (intervention) in 2029.[18]

In our reanalysis of the results of these CEAs, we changed only the prices of the therapies of interest. Because our aim was to assess the impact of drug price dynamics specifically, we did

not adjust prices for the models' other cost components, which were presumed to vary over time in line with overall medical inflation. Moreover, while the duration of exclusivity may also affect the results of CEA, we decided to focus this analysis on changes in drug price solely. We determined the impact of projected drug price dynamics according to the same year that the original CEA was conducted; we did not calculate cost-effectiveness ratios for future time points, and the incremental cost per QALY gained associated with each dynamic pricing scenario was compared with the base case from the original assessment. Sensitivity analyses involving other variables were not performed. The pricing scenarios we applied presume a US payer perspective. The models and our revised cost streams were created using Microsoft® Excel®.

Results

Tezepelumab for severe asthma

ICER reported an incremental cost effectiveness ratio of $430,300 per QALY gained for tezepelumab plus standard of care therapy as compared with standard of care therapy alone, using a fixed price for tezepelumab. We first examined how this result changed for scenarios involving biosimilar introduction after a 12-year period of exclusivity (Table 1). Post-LOE scenario A, which plateaued at a 25% reduction in drug price, yielded a cost-effectiveness ratio that was 13.2% less than the base case result, decreasing from $430,300 to $374,100 per QALY. LOE scenario B, which plateaued at a 40% price reduction, yielded a cost-effectiveness ratio that was 21.4% less than base case result, decreasing from $430,300 to $338,500 per QALY.

The improvement in cost effectiveness that occurred when incorporating post-LOE price reductions was counterbalanced by yearly drug price increases during the pre-LOE period

(Figure 1). When we combined yearly pre-LOE price increases of 2% with post-LOE scenario A, the cost-effectiveness ratio increased slightly to $444,600 per QALY gained. This result was 3.2% higher than the original assessment's base case result using a fixed drug price. When yearly pre-LOE price increases of 2% were combined with post-LOE scenario B, the incremental cost per QALY gained was $401,400, representing a 6.8% decrease from the base case in the original assessment. We also determined a "break even" rate of pre-LOE yearly price increase that would exactly offset the decrease in the cost-effectiveness ratio resulting from the two post-LOE price decrease scenarios. The offsetting rates of yearly price increase during the exclusivity period were 1.2% and 2.6% for LOE scenarios A and B, respectively.

Etanercept compared with adalimumab for rheumatoid arthritis.

ICER reported an incremental cost effectiveness ratio of $119,200 per QALY gained for etanercept as compared with adalimumab, using fixed drug prices. We first examined the effect of incorporating post-LOE price reductions for etanercept (LOE in 2029) and the comparator adalimumab (LOE in 2023), subsequent to the original assessment's starting year of 2016.

As in the tezepelumab example, we first applied the post-LOE price reduction scenarios without including yearly price increases. However, in this example the post-LOE price reduction involved both the intervention and the comparator. For post LOE scenario A, the incremental cost per QALY gained for etanercept as compared with adalimumab increased slightly from $119,200 to $121,000 per QALY (+1.6%). For post-LOE scenario B, the incremental cost per QALY gained increased slightly from $119,200 to $122,300 (+2.5%). More dramatic changes were observed when we then incorporated 2% yearly price increases for both drugs during their

period of exclusivity. Because comparator adalimumab's projected LOE of 2023 was 6 years earlier than etanercept's LOE, the additional years of accruing price increases for etanercept caused a more substantial increase in the cost-effectiveness ratio. With 2% yearly price increases for both drugs during their pre-LOE years, the cost-effectiveness ratio for etanercept as compared with adalimumab increased to $206,400 (+73.1%) for post-LOE scenario A, and increased to $195,700 (+64.1%) for post-LOE scenario B. These results are presented in Table 2.

We also determined the effect of applying the post-LOE price reduction for the comparator adalimumab but not for etanercept, given that adalimumab's projected LOE in 2023 is more immediate, while etanercept's projected LOE is several years into the future and less certain. Applying yearly 2% price increases during adalimumab's period of exclusivity and indefinitely for etanercept caused the incremental cost per QALY gained to more than double, for both post-LOE scenarios.

Discussion

The examples we present here demonstrate that price dynamics pre- and post-LOE can produce widely differing results from a base case analysis using static drug pricing. At higher levels, price increases during the period of exclusivity had a larger effect on these CEA's results than did post-LOE price reductions. The impact of post-LOE price reductions was greater for the tezepelumab example, which involved the LOE for the intervention but not the comparator. In the tezepelumab example, the post-LOE price reduction scenarios (without pre-LOE price increases) caused the cost-effectiveness ratio to decrease by 13.2-21.4%. This magnitude of change may cause an intervention to move below the cost-effectiveness threshold. However,

likely price dynamics also include price increases during the period of exclusivity. Yearly pre-LOE price increases of 2% for tezepelumab essentially wiped away the improvements gained from a post-LOE price reduction of 25%, and mostly offset the improvement resulting from a 40% post-LOE price reduction.

In the rheumatoid arthritis example, both the intervention and its comparator were presumed to lose exclusivity within 6-year timeframe. Consequently, we observed only a small percentage point change (1.6-2.5%) from the base case result when applying the post-LOE scenarios. Yet similar to what we observed for the tezepelumab example, yearly pre-LOE price increases of 2% during the period of exclusivity had a greater impact on the CEA's results, increasing the cost-effectiveness ratio by more than 60%. This magnitude of change would have shifted the cost-effectiveness ratio to above the $100,000-$150,000 per QALY health-benefit price benchmark stated in ICER's value framework.[19]

Studies examining the impacts of dynamic drug pricing on CEAs are scant, particularly regarding the effect of pre-LOE price dynamics. Schöttler et al examined the effect of drug price changes during the life cycle on the results of 4 prior published CEAs. Their updated CEA results reflected real world pricing data observed in the Netherlands, where pre-LOE drug prices decreased over time, resulting in more favorable cost effectiveness ratios than the original analyses.[20] Hoyle also noted that in the United Kingdom (UK) drug prices have decreased yearly throughout the life cycle.[21] These examples are less relevant for CEAs conducted for stakeholders in the US, where pre-LOE prices more commonly increase rather than decrease.

While research assessing the effect of pre-LOE price dynamics on the results of CEAs is limited, more research has examined the effect of post-LOE price decreases. For example, Hua et al[22] reanalyzed a CEA comparing fingolimod with interferon Beta-1a for multiple sclerosis with an

updated post-LOE price for fingolimod. The original analysis used fixed drug prices to generate an incremental cost per QALY gained of $118,434 for fingolimod compared with interferon beta-1a. When lower post-LOE drug prices were applied, the overall costs for fingolimod were lower than for the lesser-effective interferon beta-1; i.e. fingolimod dominated interferon beta -1a. The large magnitude of change in the cost effectiveness ratio reflected a LOE for fingolimod (intervention) that was assumed to occur very early in the model (year 4). CEAs for new medications will typically involve a substantially longer period of exclusivity, and thus a longer period of sizable cost differential between the new drug and its comparator. Interestingly, fingolimod's manufacturer has successfully won cases against potential generic competitors and settled other agreements outside of the courts.[23] As this example demonstrates, drug evergreening makes predicting the time of LOE more difficult, and given current practices suggests assuming longer exclusivity periods.

More frequently found in the literature are studies that redetermine a drug's cost effectiveness at a future time point after a generic has become available. For example, Cheung et al updated four CEAs of oncology drugs that became available generically in Canada.[24] The most dramatic difference they observed involved a post-LOE price decrease for erlotinib for metastatic lung cancer, which improved the cost-effectiveness ratio from $94,638 to $45,746 per QALY. In another example, Grabner et al[25] found that while atorvastatin was initially cost saving in the early years of its life cycle, its cost effectiveness worsened to a peak of roughly $45,000 per QALY gained when accounting for the introduction of generic simvastatin (comparator). While these studies highlight the potential impacts of post-LOE price reductions on the results of CEA, there is no similar body of research about the effects of yearly price increases.

US brand drug prices have increased steadily during recent years, particularly for specialty medications. For example, Savage et al found that average wholesale prices for the top 10 selling cancer drugs in 2015 increased from launch by an average of 8.8% yearly, compared with an increase of less than 0.5% for the same drugs in the UK.[5] ICER's report on unsubstantiated drug price increases between 2018-2019 highlighted examples of drugs having yearly price increases of 6% and higher that were not supported by new clinical evidence.[9] Hernandez et al[2] found that US net prices for commonly prescribed drugs increased by 4.5% yearly between 2007 to 2018, although they generally stabilized after 2015. Additionally, a 2016 investigation conducted by the Massachusetts's Attorney General's Office found that net drug prices for several disease modifying therapies for multiple sclerosis increased by more than 10% yearly between 2011-2015.[26]

While reference case guidance for how to address pre-LOE drug price dynamics in CEAs is often lacking, recommendations for addressing post-LOE price decreases are more commonly noted. The US Second Panel on Cost-Effectiveness in Health and Medicine[3] and the ISPOR Cost Task Force [27] advise analysts to consider future generics when modeling a drug's price over time. New Zealand's Methods for Cost-utility Analysis (Version 2.2) recommends that CEAs include the expected year and price reduction associated with future generics, or a "conservative proxy" thereof.[4] Yet other guidelines including ICER's reference case for Economic Evaluations,[28] and Canada's Guidelines for the Economic Evaluation of Health Technologies[29] do not specifically advise if or how to address future drug pricing dynamics. The UK's National Institute for Health and Care Excellence Guide to the Methods of Technology Appraisal states "When there are nationally available price reductions…then the reduced price should be used in

the reference-case analysis."[30] Neumann et al[1] reviewed 43 Health Technology Assessment guidelines from around the world to identify recommendations for incorporating future generic prices in CEA. Fourteen of the 43 guidelines they reviewed contained statements about using generic prices in models, and 4 guidelines, including the US Second Panel and the ISPOR Drug Cost Task Force,[27] recommend that assumptions about post-LOE prices be included in the base case. The lack of explicit recommendations in many national CEA guidelines for how to address drug price dynamics highlights that prediction of LOE can be highly speculative. More than 70% of the top selling US drugs of 2005-2015 have benefited from so called "evergreening" tactics to delay the entry of a generic version.[31] The future availability and uptake of biosimilars is additionally complicated by the challenges of manufacturing complex molecules, potentially longer approval timelines, prescriber apprehension about comparative efficacy, and heightened regulatory requirements for interchange.[32,33]

To summarize, the two examples we examined suggest that incorporating price dynamics can have varying effects on the results of CEAs depending on the magnitude of price increase during the exclusivity period, the degree of price reduction post-LOE, and the extent to which these dynamics affect the intervention and the comparator over time. Higher yearly price increases had the most substantial impact on the CEA's results, and yearly price increases beyond the degree that we assessed (4%) would further reduce the likelihood that an intervention would be considered cost effective, all other factors held equal. Incorporating post-LOE price reduction was of most consequence when affecting only the intervention but not the comparator; and presumably would also be of more consequence when affecting only the comparator but the not

the intervention. Additionally, the impact of post-LOE price reductions is further attenuated by discounting and by therapy discontinuation over time.

We suggest that CEAs that attempt to address future price dynamics should capture both pre-LOE increases and post-LOE decreases, as relevant to the analysis. However, given the substantial uncertainty about how a drug's net price will evolve over its life cycle, it seems reasonable that the effects of projected future drug prices be explored in sensitivity analyses rather than included in the base case. Moreover, as dynamics in drug prices for both interventions and comparators can dramatically affect the cost-effectiveness ratio, CEAs should be updated whenever significant changes in drug prices occur or are expected.

This study has several limitations and caveats to consider. Foremost, our analysis pertains to CEAs conducted for stakeholders within the US, where pre-LOE price increases are common. Our findings should not be generalized to other nations where pre-LOE prices are more likely to decline over time. Additionally, there is considerable uncertainty about the magnitude of price reduction that future biosimilars will achieve, and whether they will meet or exceed the degree of price reduction that we applied in our scenario analyses. Also, our examples and discussion are specific to CEAs involving chronic drug therapies that are expected to be used over many years. We provide only 2 examples; additional examples could have assessed other related dynamics such as the effects of varying time to LOE and therapy discontinuation rates. Lastly, the results presented here do not alter the findings and conclusions of the ICER assessments on these topics.

Conclusion

In these two cases incorporating price dynamics in the CEA had varied impacts on the cost-effectiveness ratio depending on the magnitude of pre-LOE price increase and post-LOE price decrease, and whether the LOE also affected the comparator. Yearly price increase magnitude during the period of exclusivity, among other factors (e.g. duration of the exclusivity period, if and when a comparator experiences LOE), may counterbalance the effects of lower post-LOE intervention prices.

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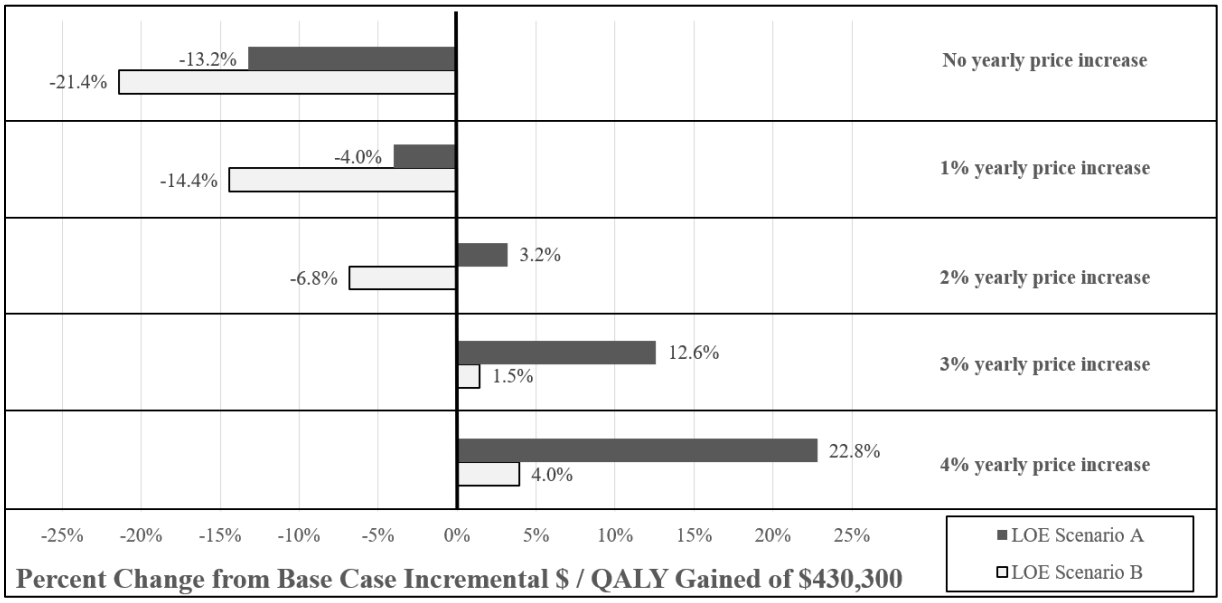
Figure 1. Percent Change from the Base Case Incremental Cost per QALY when Incorporating Future Drug Price Scenarios for Tezepelumab for Severe Asthma



LOE = Loss of Exclusivity
LOE Scenario A: 10% decrease in first year of loss of exclusivity, followed by a 25% decrease in second year carried forward
LOE Scenario B: 20% decrease in first year of loss of exclusivity, followed by a 40% decrease in second year carried forward

Table 1. Incremental Costs per QALY for Tezepelumab for Severe Asthma Plus Standard of Care versus Standard of Care Alone, Incorporating Future Drug Price Scenarios

Yearly price increases during 12 years of exclusivity	Price Reduction Following Loss of Exclusivity (LOE)	
	Scenario A: 10% price decrease in year 1 followed by a 25% decrease in second year carried forward	Scenario B: 20% price decrease in year 1 followed by a 40% decrease in second year carried forward
	Cost per QALY (% change from base case of $430,300/QALY)	
0%	$ 374,100 (-13.2%)	$ 338,500 (-21.4%)
1%	$ 413,500 (-4.0%)	$ 368,700 (-14.4%)
2%	$ 444,600 (+3.2%)	$ 401,400 (-6.8%)
3%	$ 485,100 (+12.6%)	$ 437,100 (+1.5)
4%	$ 529,200 (+22.8%)	$ 448,000 (+4.0)

Table 2. Results for Example 2: Incremental Cost per QALY Gained and Percent Change from Base Case for Future Price Scenarios for Etanercept and Adalimumab (Comparator) for Rheumatoid Arthritis.

Yearly price increase until LOE	Price reduction scenarios for LOE of etanercept in 2029 and adalimumab (comparator) in 2023		Price reduction scenarios for LOE of comparator adalimumab in 2023 but no LOE for etanercept	
	Cost per QALY (% change from the base case of $119,200/QALY)			
	LOE Scenario A	LOE Scenario B	LOE Scenario A	LOE Scenario B
0%	$ 121,000 (+1.6%)	$ 122,300 (+2.5%)	$ 162,300 (+36.1%)	$ 205,400 (+72.3%)
2%	$ 206,400 (+73.1%)	$195, 700 (+64.1%)	$ 285,400 (+139.4%)	$ 334,900 (+180.9%)
4%	$ 284,700 (+138.8%)	$ 274,000 (+129.8%)	$ 418,900 (+251.3%)	$ 465,300 (+290.2%)

LOE = Loss of exclusivity; LOE Scenario A: 10% decrease in first year of loss of exclusivity, followed by a 25% decrease in second year carried forward; LOE Scenario B: 20% decrease in first year of loss of exclusivity, followed by a 40% decrease in second year carried forward; The model starting year was 2016