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CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

Guselkumab (Tremfya)

(Janssen Inc.)

Indication: For the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

BSC	best supportive care
CDR	CADTH Common Drug Review
CUA	cost-utility analysis
EQ-5D-5L	EuroQol 5 Dimension 5 Level
EQ-PSO	EuroQol 5 Dimension Psoriasis Bolt-On
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
ICUR	incremental cost-utility ratio
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
PASI	Psoriasis Area and Severity Index
PSOLAR	Psoriasis Longitudinal Assessment and Registry
QALY	quality-adjusted life-year
SC	subcutaneous

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Guselkumab (Tremfya) 100 mg/mL pre-filled syringe
Study Question	Is guselkumab cost-effective compared with approved biologic therapies for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy?
Type of Economic Evaluation	Cost-utility analysis
Target Population	Adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.
Treatment	Guselkumab 100 mg SC at weeks 0 and 4, followed by every 8 weeks thereafter
Outcome	Quality-adjusted life-years (QALYs)
Comparator(s)	• Adalimumab (Humira) • Etanercept (Enbrel) • Infliximab (Remicade/Inflectra) • Ixekizumab (Taltz) • Secukinumab (Cosentyx) • Ustekinumab (Stelara)
Perspective	Canadian public health care payer
Time Horizon	Ten years
Results for Base Case	• Based on the manufacturer's probabilistic analysis, guselkumab was less costly and more effective (i.e., gained more QALYs) when compared with adalimumab, etanercept, infliximab, secukinumab, and ustekinumab. • Guselkumab was less costly but less effective when compared with ixekizumab. The incremental cost per QALY gained for ixekizumab versus guselkumab was $121,255. • Guselkumab had the highest probability of being cost-effective given a willingness to pay threshold of $50,000 per QALY was 41.9%.
Key Limitations	• The manufacturer assumed continued efficacy beyond the time horizon of the clinical trials (up to 48 weeks). No assumption with respect to the waning of treatment effect was included. • Uncertainty with the manufacturer-commissioned indirect treatment comparison estimates for treatment efficacy. The CDR clinical review strongly questioned the importance of the adjusted analysis in that it only takes into account the difference in placebo response rates rather than looking at all of the potential effect modifiers. The adjusted analysis strongly biased the results in favour of guselkumab. • The manufacturer assumed differential adverse event and discontinuation rates favouring guselkumab when no available data to support this benefit of guselkumab. • Utility values used in the analysis were obtained from a less reliable instrument (EQ-PSO) when data for EQ-5D-5L were available. This biased results in favour of guselkumab. • The manufacturer assumed differential time points for treatment effectiveness would be assessed based on the timing of assessment in randomized controlled trials. • The options for second- and third-line therapy considered in the analysis did not appear appropriate. • The submitted model lacked transparency and was unnecessarily complex, which made both the assessment of validity and the ability to conduct reanalysis highly challenging.

CDR Estimate(s)	• CDR reanalysis of the manufacturer's base case addressed all issues except waning of treatment effect.
	• Guselkumab was not a cost-effective treatment for adult patients with plaque psoriasis when considering all available therapies.
	  ○ Guselkumab was dominated by ixekizumab.
	  ○ The incremental cost per QALY gained for guselkumab versus infliximab was $1.6 million.
	  ○ The probability that guselkumab was cost-effective at a willingness to pay threshold of $50,000 per QALY was 11.9%.

CDR = CADTH Common Drug Review; EQ-PSO = EuroQol 5 Dimension Psoriasis Bolt-On; EQ-5D-5L = EuroQol 5 Dimension 5 Level; QALY = quality-adjusted life-year; SC = subcutaneous.

Drug	Guselkumab (Tremfya)
Indication	For the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy
Reimbursement request	Treatment of adult patients with moderate-to-severe plaque psoriasis
Dosage form(s)	100 mg/mL pre-filled syringe
NOC date	November 10, 2017
Manufacturer	Janssen Inc.

Executive Summary

Background

Guselkumab (Tremfya) is a fully human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody that binds selectively to the interleukin 23 (IL-23) protein with high specificity and affinity.[1] Levels of IL-23 are elevated in the skin of patients with plaque psoriasis and guselkumab exerts its clinical effects in plaque psoriasis through blockade of the IL-23 cytokine pathway. The proposed indication submitted to Health Canada for guselkumab is for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.[2] The proposed recommended dose is 100 mg to be given as subcutaneous (SC) injection at week 0 and week 4, followed by maintenance dosing every eight weeks thereafter.[1] The price is $3,060 per 100 mg/mL pre-filled syringe.

The manufacturer submitted a cost-utility analysis based on a Markov state-transition model comparing guselkumab with currently available treatments for adult patients with plaque psoriasis.[3] Comparators included adalimumab, etanercept, infliximab, ixekizumab, ustekinumab, and secukinumab. The model structure was simplistic. At the end of a treatment induction period, patients were assigned to a health state based on the Psoriasis Area and Severity Index (PASI) score (less than 50; 50 to 74; 75 to 89; 90 to 99; and 100). Patients with a PASI score of less than 75 moved to the next line of therapy. If the PASI score was greater than and equal to 75 the patient stayed in that state for the remainder of the time horizon except when they died or discontinued treatment. All-cause mortality rates and treatment-specific discontinuation rates were applied to each cycle and were independent of PASI score. Second- and third-line therapies were considered and were hybrids of the therapies considered for first line as comparators. After third-line patients transition to best supportive care (BSC). Data on PASI scores were obtained from a manufacturer-commissioned unpublished network meta-analysis with results adjusted by

placebo rates.[4] Mortality was based on Canada all-cause mortality data. Discontinuation rates were obtained from a published analysis.[5] No data were available for guselkumab so the discontinuation rate for ustekinumab was assumed. Rates of adverse events were obtained from a published study.[6] No data were available for guselkumab so the average adverse event rate for ustekinumab was assumed. Costs included were drug costs, costs of adverse events, physician visits, and laboratory tests. The clinical trials of guselkumab did not include utility assessments. Baseline utility was derived from a National Institute for Health and Care Excellence (NICE) technology assessment.[7] Data by PASI score was derived from a study by Pickard through the EuroQol 5 Dimension Psoriasis Bolt-On (EQ-PSO) instrument.[8,9]

The manufacturer-estimated costs and quality-adjusted life-years (QALYs) for each therapy through probabilistic analysis. Guselkumab was found to be less costly and more effective (i.e., gained more QALYs) when compared with adalimumab, etanercept, infliximab, secukinumab, and ustekinumab. Ixekizumab was more effective and more costly when compared with guselkumab; resulting in an incremental cost per QALY gained for ixekizumab of $121,255 compared with guselkumab. Guselkumab had the highest probability of being cost-effective given a willingness to pay threshold of $50,000 per QALY was 41.9%. Probabilities for other therapies were 36.7% for infliximab; 20.9% for ixekizumab; and 0.6% for secukinumab.

Summary of Identified Limitations and Key Results

The key limitations of the manufacturer's economic evaluation identified by CDR were focused primarily on the availability of clinical information and on assumptions that were largely in favour of guselkumab. The comparative clinical efficacy inputs relating to PASI score were sourced from a manufacturer-commissioned network meta-analysis. The primary issue identified by CDR clinical reviewers was the use of an adjusted analysis for placebo response rates that strongly favoured guselkumab over the unadjusted analysis. The clinical expert consulted for this review stated that the most important effect modifiers were weight, previous biologic use, and disease severity, which contradicts the manufacturer's approach. Assumptions were made regarding the duration of treatment effect: at the end of the induction period and from that period onwards there were no further changes in PASI score and treatment efficacy was maintained for a patient's lifetime. The manufacturer indicated that applying discontinuation rates addresses this concern; however, this does not change the proportion of patients on active treatment by PASI score category over time. Finally, there is no data available to inform the adverse event and long-term discontinuation rates for guselkumab. The manufacturer assumed that the rates for ustekinumab could be applied to guselkumab. This was highly favourable for guselkumab. The CDR clinical expert suggested that assuming equal discontinuation rates for all therapies was more appropriate and that the average adverse event rates may be more appropriate.

CDR identified several other parameters of uncertainty, including: health state utility values; time when patient response was assessed; and choice of second- and third-line therapies. These parameters were considered in combination with the primary limitations in defining the CDR base case. However, given the overly complex nature of the model, it was not possible to incorporate alternative assumptions relating to continued treatment efficacy.

CDR found that guselkumab was not a cost-effective treatment for adult patients with plaque psoriasis when considering all available therapies. Guselkumab was dominated by ixekizumab. In addition, the incremental cost per QALY gained for guselkumab versus

infliximab was $1.6 million. Results demonstrated a high degree of uncertainty, with a probability that guselkumab was cost-effective at a willingness to pay threshold of $50,000 per QALY of 11.9%. If the price of guselkumab was reduced by 5.4%, guselkumab would be associated with an incremental cost per QALY gained of $50,000 compared with infliximab. However, results were very sensitive to potential price reductions for other biologics. For example, guselkumab would be dominated by secukinumab were the price of secukinumab 1% lower than the price considered in the analysis.

Conclusions

Based on CDR reanalyses, guselkumab is not a cost-effective treatment for adult patients with plaque psoriasis. Guselkumab was found to have an 11.9% probability of being cost-effective at a willingness to pay threshold of $50,000 per QALY. Infliximab was the optimal therapy at a willingness to pay threshold of less than $219,387 per QALY gained. If a decision-maker's willingness to pay for a gain in QALY is greater than $219,387, then ixekizumab is the optimal therapy.

A reduction in the submitted price of 5.4% or greater could result in an incremental cost-utility ratio (ICUR) of less than $50,000 per QALY for guselkumab. However, results would differ substantially if negotiated price reductions for any of the comparators were considered, as the price of comparators is a key driver of the results.

It should be noted that the economic model submitted by the manufacturer was unnecessarily complex and lacked transparency, which made both the assessment of validity and the ability to conduct reanalysis challenging. This, combined with the inability to assess the impact of the waning of treatment effect, resulted in uncertainty regarding the results of the analysis. Given the lack of significant differences in efficacy between guselkumab and comparators, and the modest QALY differences between these agents, there appears to be limited justification for a price premium for guselkumab.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer submitted an economic model which estimated the costs and quality-adjusted life-years gained for alternative treatments for plaque psoriasis. The model compared the cost-effectiveness of guselkumab and other biologic therapies reimbursed in Canada: adalimumab, etanercept, infliximab, ixekizumab, ustekinumab, and secukinumab.[3] The target population was adult patients with plaque psoriasis, as in the VOYAGE 1 and VOYAGE 2 clinical trials.[10,11] The modelled patients were on average assumed to be 44 years old at the time of entry into the model; patients were also predominantly male (71.1%), with a mean weight of 89.1 kg (24.1% greater than 100 kg).

The model was run using 28-day cycles over a 10-year time horizon in the base case. All costs and outcomes were discounted at an annual rate of 1.5% and the analysis was conducted from the perspective of the Canadian publicly funded health care system.

Model Structure

Analysis was conducted using a cohort multi-state Markov model developed in Microsoft Excel. The model was composed of two time periods for each line of treatment: 1) the time period up to initial assessment: (during this period the cohort was simply subject to underlying age- and gender-specific mortality); and 2) the time period post assessment. At the point of assessment, the cohort was divided by Psoriasis Area and Severity Index (PASI) score based on the data from the network meta-analysis (NMA). Individuals with a PASI score less than 75 would be allocated to second-line therapy and the same process as described previously begins again. For those with a PASI score greater than and equal to 75, it was assumed that for each cycle three events could occur: the patient could discontinue treatment based on a discontinuation rate independent of PASI score; the patient could die based on the underlying age- and gender-specific mortality; or, the patient could remain in the same PASI score state. Note that no transitions between PASI scores are modelled. Those who discontinue therapy would then move to second-line therapy. Patients can transition from initial therapy to second-line therapy, third-line therapy, and finally best supportive care (BSC).

Model Inputs

For first-line treatments, the time to assessment was assumed to be either 12 weeks (etanercept, infliximab, ixekizumab, secukinumab, and ustekinumab) or 16 weeks (guselkumab and adalimumab). At the assessment time, the cohort was allocated to PASI score based on the manufacturers submitted NMA [redacted].[4]

The annual probability for discontinuation for adalimumab, etanercept, infliximab and ustekinumab were obtained from an analysis of the Psoriasis Longitudinal Assessment and Registry (PSOLAR) database.[5] As first-line therapy this was 15%, 12%, 11%, and 4.7% respectively. Data for other biologics including guselkumab were not available, and the probability for ustekinumab was assumed to apply. Annual probabilities were then converted to 28-day probabilities and applied to patients with PASI score greater than and equal to 75.

Adverse events modelled were restricted to serious infections with annual rates for adalimumab, etanercept, infliximab and ustekinumab obtained from an analysis of the PSOLAR database:[6] 1.97, 1.47, 2.49, and 0.83 per 100 patient-years, respectively. Data for other biologics including guselkumab were not available and the rate for ustekinumab was assumed to apply. Annual rates were then converted to 28-day probabilities and applied to patients on therapy.

Second-line and third-line therapy was assumed to consist of average of biologic therapies weighted as follows: 27.7% to adalimumab; 25% to etanercept; 7.2% to infliximab; 0.6% to secukinumab; and 39.5% to ustekinumab. These were derived from unpublished data.[12] Treatment effectiveness was derived as a weighted effectiveness based on the effectiveness data from the NMA.[4] Discontinuation probabilities and adverse event probabilities were the weighted sum of data from analysis of the PSOLAR Database.[5,6]

BSC was assumed to consist of combination therapy with biologics and traditional systemic therapies. The probability of adverse events was based on the average of all biologics and non-biologic therapies from the analysis of the PSOLAR database.[4] The effectiveness of BSC was assumed to be the same as second- and third-line therapy.

Health state utilities in the model were based on PASI score (a baseline utility at onset of treatment followed by increments for PASI response: less than50, 50 to 74, 75 to 89, 90 to 99,100) and the incidence of severe infections. A common baseline utility was applied to all treatments and was derived from a National Institute for Health and Care Excellence (NICE) technology appraisal.[5] As a common baseline was applied, the choice of baseline did not affect the incremental results. The increments by PASI score were informed by a systematic review which identified two studies providing six alternative estimates.[8,13] The model adopted values derived from an analysis of clinical trial data applying the EuroQol 5 Dimensions Psoriasis Bolt-On (EQ-PSO) instrument.[8,9] The disutility for severe infections was derived from the published literature and adjusted for the duration of the infection.

Costs included were those for disease management (physician visits and laboratory fees), administration and monitoring costs, drug acquisition costs (excluding dispensing fees or markups), and costs of severe infections. All costs were reported in 2017 Canadian dollars. For second- and third-line therapy, a weighted average costs of biologic therapy was applied. For BSC, costs were based upon a study by Fonia and involved applying the average unit costs of therapy prior to the introduction of biologic therapy in addition to costs of biologics based on the second- and third-line therapy.[14]

Mortality was based on Canada all-cause mortality data.

The manufacturer highlighted the following assumptions within their model:

- PASI response achieved at the end of the induction period is maintained throughout treatment (i.e., maintenance period). In other words, a patient cannot transition between PASI levels when on a given therapy.
- Patients remain on a given biologic therapy during the entire induction period (i.e., no discontinuation during induction).
- Baseline utility value is the same across all lines of treatment.
- Utility gains associated with treatment response (i.e., PASI response) are only achieved in the maintenance phase and are not treatment-specific.
- Patients receive three lines of biologic therapy before transitioning to BSC as the final line of therapy.

- Probability of discontinuing newer agents (guselkumab, secukinumab, ixekizumab) from the maintenance period is the same as ustekinumab based on PSOLAR.
- Efficacy of a biosimilar is identical to the brand name biologic unless published, psoriasis-specific data are available.
- Efficacy for a given therapy is the same in all lines of treatment (i.e., second, third, and final line).
- BSC was assumed to consist of biologics in combination with systemic therapies and phototherapy.
- Serious infection rates of newer therapies (guselkumab, secukinumab, ixekizumab) are the same as those of ustekinumab based on PSOLAR.
- Risk of death is a factor of sex and age alone (i.e., general population mortality data used).
- 93% of infliximab use is subsequent entry biologic (Inflectra).

Manufacturer's Base Case

The manufacturer reported that guselkumab was associated with a 10-year cost of $198,332 and 7.25 quality-adjusted life-years (QALYs) over the model time horizon (Table 2). Guselkumab dominated adalimumab, etanercept, ustekinumab, and infliximab in the base case, i.e., guselkumab was associated with lower total costs and greater QALYs gained when compared with these treatments. Detailed breakdown of costs are provided in the Appendix (Table 8).

When compared with ixekizumab, guselkumab was associated with lower costs and lower QALYs. The incremental cost per QALY gained from ixekizumab was $121,255 per QALY when compared with guselkumab.

Table 2: Summary of Results of the Manufacturer's Base Case

	Total Costs ($)	Total QALYs	Incremental Cost per QALY Gained vs. Guselkumab	Sequential ICER
Non-Dominated Options				
Guselkumab	$ 198,332	7.25		
Ixekizumab	$ 200,374	7.27	$ 121,255	$ 121,255
Dominated Options				
Adalimumab	$ 209,526	7.08	Dominated	Dominated by: ustekinumab, infliximab, secukinumab guselkumab and ixekizumab
Etanercept	$ 216,703	7.09	Dominated	Dominated by: ustekinumab, infliximab, secukinumab, guselkumab, and ixekizumab
Ustekinumab	$ 206,255	7.13	Dominated	Dominated by: infliximab, secukinumab, guselkumab, and ixekizumab
Infliximab	$ 199,893	7.16	Dominated	Dominated by: guselkumab
Secukinumab	$ 201,196	7.21	Dominated	Dominated by: guselkumab and ixekizumab

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.
Note: All costs are presented in 2017 Canadian dollars.
Source: Total costs, and QALYs are probabilistic values, as reported in the manufacturer's submission report and the original economic model submitted to CADTH.[3]

Thus, guselkumab was found to be the optimal therapy unless a decision-maker was willing to pay more than $121,255 per QALY gained. If a decision-maker is willing to pay this amount, ixekizumab would be the optimal therapy.

Summary of Manufacturer's Scenario Analyses

The manufacturer conducted a range of scenario analyses. Under each scenario, results in terms of costs and QALYs were estimated using probabilistic analysis.

The following scenarios were considered:

- Analysis used the [redacted] results from the NMA. In this analysis, guselkumab was found to be subject to extended dominance through infliximab and ixekizumab.
- Analysis adopted a societal perspective. In this analysis the incremental cost per QALY gained for ixekizumab versus guselkumab was reduced to $85,874.
- Analysis assumed reduced efficacy in subsequent lines of therapy. In this analysis the incremental cost per QALY gained for ixekizumab versus guselkumab was reduced to $120,058.
- Analysis assumed adverse events were obtained from a baseline risk adjusted NMA. In this analysis the incremental cost per QALY gained for ixekizumab versus guselkumab increased to $178,992.
- Analysis adopted alternative discount rates of 0% and 3%. In these analyses the incremental cost per QALY gained for ixekizumab versus guselkumab was $118,476 and $132,549, respectively.

Further deterministic sensitivity analyses were conducted but were not reported in a meaningful manner in that the incremental cost per QALY gained for ixekizumab versus guselkumab was not provided.

Limitations of Manufacturer's Submission

CDR identified the following key limitations of the manufacturer's model:

Reliance on [redacted] data from the network meta-analysis: Efficacy inputs relating to PASI score were sourced from a manufacturer-commissioned NMA.[4] [redacted] The clinical expert consulted for this review stated that the most important effect modifiers were weight, previous biologic use, and disease severity [redacted]. Based on the above, the CDR base case adopted the [redacted] results from the NMA.

Duration of treatment efficacy: Within the model it is assumed that the efficacy of treatment was applied in the model at the end of the induction period and from that period onward there were no further changes in PASI score. Thus the underlying assumption is that the treatment efficacy is maintained for the duration of the analysis. This assumption needs to be seriously questioned and any assumptions relating to waning of treatment effect would likely have significant effect on the study results.

The manufacturer indicated that applying discontinuation rates addresses this concern. This is not a defensible argument in that applying a discontinuation rate did not change the proportion of patients on active treatment by PASI score category. If treatment effect is subject to waning, the proportion of patient's in the more preferable sates based on PASI score would likely decrease with time reducing the QALY gains from therapy. Given the design of the model it was not possible to incorporate alternate assumptions addressing this issue.

Lack of data for adverse event and discontinuation rates with guselkumab: No data were available to inform the adverse event and long-term discontinuation rates for guselkumab. The manufacturer adopted an assumption that the rates for ustekinumab (which had the lowest rates for both) could be applied to guselkumab. This was highly favourable for guselkumab. The CDR clinical expert suggested that assuming equal discontinuation rates for all therapies was more appropriate and that the average adverse event rates may be more appropriate. Thus, within the CDR base analysis an annual discontinuation rate of 10% is applied to all therapies and an annual rate of severe infection of 1.45 is applied to all therapies for which data were unavailable.

Increments in utility values based on PASI response: The incremental effect of PASI response on utility values was derived from a study by Pickard.[8] The analysis adopted utility values which were derived using the EQ-PSO, a version of the EQ-5D which includes bolt-on option for psoriasis.[7] However, the value set for the EQ-PSO was obtained from a very small sample size and the underlying uncertainty around this value set is unclear. Furthermore, the validity and reliability of this instrument has only been assessed in a limited fashion.[9] Thus, CDR felt that analyses using the EQ-5D-5L scoring algorithm would be preferred. It should be noted that analysis using the EQ-PSO favoured guselkumab.

Differential timing of assessment: The manufacturer assumed that there was differential timing of assessment for each treatment. For first-line treatments, the time to assessment was assumed to be either 12 weeks (etanercept, infliximab, ixekizumab, secukinumab, and ustekinumab) or 16 weeks (guselkumab and adalimumab). At the assessment time, the cohort was allocated to PASI score based on the manufacturers submitted NMA and patients were then subject to treatment discontinuation. Thus, the differential timing would likely impact the results of the analysis. CDR reanalysis adopted a consistent time point for assessment (16 weeks) for each biologic.

Choice of second- and third-line therapies and BSC: Analysis assumed a consistent second- and third-line therapy for each biologic. This was characterized as hybrid therapy derived by weighting parameters for current biologics by unpublished data of current usage: 27.7% adalimumab; 25% etanercept; 7.2% infliximab; 0.6% secukinumab; and, 39.5% ustekinumab (IMS Brogan 2017). Treatment effectiveness was derived as a weighted effectiveness based on the effectiveness data from the NMA. Discontinuation probabilities and adverse event probabilities were the weighted sum of data from analysis of the PSOLAR Database.[5,6] Costs were derived as weighted treatment costs. BSC was assumed to consist of combination therapy with biologics and traditional systemic therapies. The probability of adverse events was based on the average of all biologics and non-biologic therapies from the analysis of the PSOLAR database.[6] The effectiveness of BSC was assumed to be the same as second- and third-line therapy. Costs were derived by applying the average unit costs of therapy prior to the introduction of biologic therapy in addition to costs of biologics based on the second- and third-line therapy.[14]

There were numerous problems with this approach. The main issue was that second-line effectiveness incorporated the effectiveness of all first-line therapies so data incorporated the effectiveness of the specific first-line therapy of interest. A further problem was that the cost of BSC was argued to be higher than the costs of any biologic which lacked face validity. CDR contends that the manufacturer needed to provide a more thoughtful approach to determining the appropriate future-line therapies. Based on these concerns, CDR excluded second- and third-line therapies from the analysis.

Lack of transparency and functionality of the manufacturer's submitted model: The submitted model had several issues that made validation and evaluation more difficult than necessary. In particular, the model did not allow CDR to switch between probabilistic and deterministic mode, as was requested of the manufacturer. This is essential for assessing the validity of the probabilistic analysis. The model was overly complex in that it incorporated unnecessary analysis which significantly increased the run time of the model, thus affecting the ability to both conduct reanalysis and assess the validity of the model. CDR requested that the manufacturer provide only as complex a model as necessary. The manufacturer made some changes to the model upon requests from CDR, however these did not fully address issues of model complexity. Thus, simple reanalyses adopting alternative assumptions were challenging to conduct and verify.

CADTH Common Drug Review Reanalyses

As noted in the limitations, CDR identified several key limitations relating to the manufacturer's model. CDR presents a revised probabilistic analysis (CDR base case) in Table 3 with alterations based on these limitations. The modifications made to the manufacturer-submitted model include:

- Use of the [redacted] NMA results
- Equal probability of discontinuation for all therapies
- Average rates of serious infection for all therapies where data were unavailable
- Use of EQ-5D-5L utility values
- Same assessment point for all biologics
- Exclusion of second- and third-line therapies

Based on a sequential probabilistic analysis of the CDR base case (Table 3), CDR found that guselkumab was not a cost-effective treatment for patients with plaque psoriasis when considering all available treatments (Figure 3). At a willingness to pay threshold of $50,000 per QALY gained, guselkumab had an 11.9% probability of being cost-effective. Sequential analysis further revealed that infliximab was the optimal therapy at a willingness to pay threshold less than $219,387 per QALY gained. If a decision-maker's willingness to pay for a gain in QALY is greater than $219,387, then ixekizumab is the optimal therapy. Guselkumab was dominated by ixekizumab: guselkumab is more costly and associated with fewer QALYs than ixekizumab.

The incremental cost per QALY gained for guselkumab versus infliximab was $1.6 million. The high incremental cost per QALY gained for guselkumab versus infliximab is the result of the small, incremental QALYs gained from guselkumab compared with infliximab (0.0035).

Table 3: CDR Base Case

	Total Costs ($)	Total QALYs	Incremental Cost per QALY Gained vs. Infliximab	Sequential ICER
Infliximab	$ 210,828	6.93		
Ixekizumab	$ 216,091	6.96	$ 219,387	$ 219,387
Dominated Options				
Etanercept	$ 233,596	6.87	Dominated	Dominated by: adalimumab, ustekinumab, infliximab, secukinumab, guselkumab, and ixekizumab
Adalimumab	$ 222,704	6.89	Dominated	Dominated by: ustekinumab, infliximab, secukinumab, guselkumab, and ixekizumab
Ustekinumab	$ 221,340	6.90	Dominated	Dominated by: infliximab, secukinumab, guselkumab, and ixekizumab
Guselkumab	$ 216,453	6.94	$ 1,606,003	Dominated by: ixekizumab
Secukinumab	$ 217,283	6.94	$ 1,280,056	Dominated by: ixekizumab

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

The parameters that were the greatest driver of results were: the use of the adjusted NMA results, the choice of discontinuation probabilities, and the choice of utility values. A detailed summary and critical appraisal of the NMA is presented in the CDR Clinical Review Report.

CDR explored the impact of price reductions on the CDR base-case analysis. Using the CDR base-case analysis, a price reduction for guselkumab of about 5.4% was required for guselkumab to be considered the optimal therapy at a willingness to pay of $50,000 per QALY.

However, results were very sensitive to any negotiated price reductions for other therapies (Table 9). For example, a less than 1% reduction in the price of secukinumab would lead to secukinumab dominating guselkumab. Furthermore, a 10% price reduction for ustekinumab would lead to the incremental cost per QALY gained for guselkumab versus ustekinumab being greater than $100,000.

Patient Input

Patient input was received from two groups: the Canadian Skin Patient Alliance and the Arthritis Consumer Experts. Patients with psoriasis experience scales and plaques that can occur anywhere on their bodies, citing the most significant physical symptoms of: scales, flaking, itching, skin cracking and bleeding, pain, and joint pain. The impact of these physical symptoms can result in psychological effects: embarrassment, shame, self-confidence issues, anxiety, and depression. Patients may isolate themselves from social interaction or refrain from participating in different activities such as dancing, swimming, and sports that would expose the affected parts of the skin. Most patients try to hide their lesions, with some wearing particular clothing (e.g., pants rather than skirts, no bathing suits) or wearing their hair in a certain manner for coverage. Sleep can be negatively affected, both due to the physical symptoms and psychological symptoms. The manufacturer captured these aspects by defining health states based on PASI scores, with utility values capturing the preferences for these states.

It was noted that caregivers of patients with psoriasis often experience increases in the amount of care and household cleaning. In addition, some patients require help to apply creams, go to phototherapy appointments, or travel to infusion clinics (e.g., should the patient be on infusion biologics). Caregivers often find themselves negatively affected psychologically and dysfunctional, as the whole family tends to absorb the shame, depression, and isolation associated with the disease. As the analysis was taken from the perspective of the public health care payer, caregiver aspects were not included.

Conclusions

Based on CDR reanalysis, guselkumab was not cost-effective when considering all available treatments for patients with moderate-to-severe plaque psoriasis. Guselkumab had an 11.9% probability of being cost-effective at a willingness to pay threshold of $50,000 per QALY. Infliximab was the optimal therapy at a willingness to pay threshold less than $219,387 per QALY gained. If a decision-maker's willingness to pay for a gain in QALY is greater than $219,387, then ixekizumab is the optimal therapy. CADTH noted modest QALY differences between these agents.

Given a 5.4% reduction in its submitted price, guselkumab would be considered the optimal therapy if a decision-maker's willingness to pay is at least $50,000 per QALY. However,

results would differ substantially if negotiated price reductions for any of the comparators were considered, as the price of comparators is a key driver of the results.

The complex approach taken for the model, which lacked transparency, made both the assessment of validity and the ability to conduct reanalysis challenging. This, combined with the inability to assess the impact of the waning of treatment effect created uncertainty regarding the results of the analysis. Given the lack of significant differences in efficacy between guselkumab and comparators, and the modest QALY differences between these agents, there appears to be limited justification for a price premium for guselkumab.

Appendix 1: Cost Comparison

The comparators presented in Table 4 have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice, versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in Table 4 and as such may not represent the actual costs to public drug plans.

Table 4: CDR Cost Comparison Table for the Treatment of Plaque Psoriasis

Drug / Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Annual Drug Cost ($)
Guselkumab (Tremfya)	100 mg/mL	pre-filled syringe	$3,059.7400[a]	100 mg SC at weeks 0 and 4, followed by every 8 weeks thereafter	First year: $21,418 Subsequent years: $19,943
Other Biologics					
Adalimumab (Humira)	40 mg/0.8 mL	syringe or pen	$769.9700	80 mg initial dose, 40 mg every other week starting one week after initial dose	First year: $21,559 Subsequent years:$20,074
Etanercept (Enbrel)	50 mg/mL 25 mg/vial	syringe or pen vial	$405.9850 $202.9300	50 mg twice weekly for 12 weeks, then 50 mg weekly	First year: $25,983 Subsequent years: $21,169
Infliximab (Remicade)	100 mg/vial	vial	$977.0000[b]	5 mg/kg/dose, for 3 doses (0, 2, and 6 weeks) then 5 mg/kg every 8 weeks	First year: $39,080[c] Subsequent years: $31,840[c]
Infliximab (Inflectra)			$525.0000		First year: $21,000[c] Subsequent years: $17,063[c]
Ixekizumab (Taltz)	80 mg/ 1mL	Pre-filled syringe	$1,519.0000[d]	160 mg initial dose; 80 mg at 2, 4, 6, 8, 10, and 12 weeks; followed by 80 mg every four weeks	First year:$25,823 Subsequent years: $19,801
Secukinumab (Cosentyx)	150 mg/mL	pre-filled syringe or pen	$822.5000	300 mg SC injection at weeks 0, 1, 2, and 3, then monthly injections starting at week 4	First year: $24,675 Subsequent years: $19,740
Ustekinumab (Stelara)	45 mg/0.5 mL 90 mg/1 mL	pre-filled syringe	$4,593.1400	< 100 kg patients: 45 mg at weeks 0 and 4, followed by 45 mg every 12 weeks thereafter (same for > 100 kg, at 90 mg)	First year: $22,966 Subsequent years: $19,958
Conventional Systemic Treatments					
Methotrexate	2.5 mg 10 mg 20 mg/2 mL 50 mg/2 mL	tablet tablet vial vial	$0.6325 $2.7000[b] $12.5000 $8.9200	10 mg to 25 mg by mouth or IM weekly	$141 to $330 $233 to $325
Cyclosporine (generics)	10 mg 25 mg 50 mg 100 mg	caplet	$0.6238 $0.9952 $1.9400 $3.8815	2.5 to 5 mg/kg daily, in 2 divided doses	$3,197 to $7,083[c]
Acitretin (Soriatane)	10 mg 25 mg	caplet	$2.5930 $4.5540	25 mg to 50 mg daily	$1,662 to $3,324
Phosphodiesterase-4 Inhibitor					
Apremilast (Otezla)	30 mg	tablet	$19.5714[e]	30 mg twice daily	First year: $14,287

IM = intramuscular; SC = subcutaneous.

Note: All prices are from the Ontario Drug Benefit Formulary[15] (accessed September 2017), unless otherwise indicated, and do not include dispensing fees.

[A] Manufacturer's submitted price.

[b] Saskatchewan formulary[16] (September 2017).

[c] Assumes patient weight of 90kg and wastage of excess medication in vials, if applicable.

[d] Wholesale price Newfoundland[17] and Quebec,[18] IMS Quintiles Delta PA[19] (September 2017).

[e] Wholesale price nationwide, IMS Quintiles Delta PA[19] (September 2017).

Appendix 2: Additional Information

Table 5: Submission Quality

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?			X
Comments Reviewer to provide comments if checking “no”	As noted in the limitations section, there were concerns with the lack of transparency within the model and an inability to verify the methods of the probabilistic analysis		
Was the material included (content) sufficient?			X
Comments Reviewer to provide comments if checking “poor”	CADTH requested that the manufacturer provide an updated model which was more transparent, excluded unnecessary complexities, and provided the ability to move between probabilistic and deterministic analysis. The manufacturer made some changes to the model but these did not fully address the requests made by CDR.		
Was the submission well organized and was information easy to locate?		X	
Comments Reviewer to provide comments if checking “poor”	None		

Table 6: Author Information

Authors of the Pharmacoeconomic Evaluation Submitted to CDR

☐ Adaptation of Global model/Canadian model done by the manufacturer

☒ Adaptation of Global model/Canadian model done by a private consultant contracted by the manufacturer

☐ Adaptation of Global model/Canadian model done by an academic consultant contracted by the manufacturer

☐ Other (please specify)

	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document			X
Authors had independent control over the methods and right to publish analysis			X

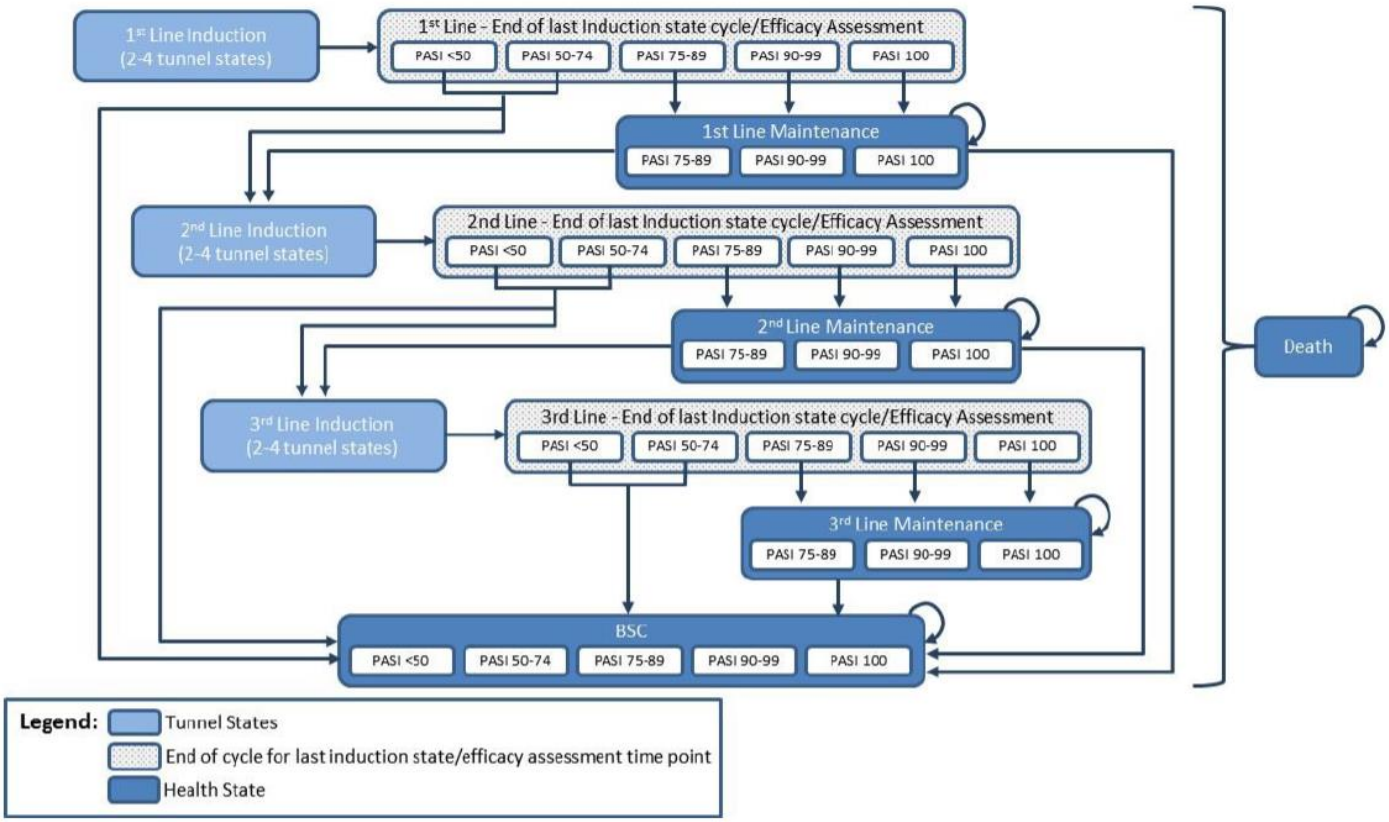
Appendix 3: Health Technology Assessment Reviews of Drug

Note there are no reviews for guselkumab conducted by health technology assessment organizations that had been completed at the time of this review. Guselkumab is currently undergoing review at the National Institute for Health and Care Excellence (NICE).

Appendix 4: Reviewer Worksheets

Manufacturer's Model Structure

Figure 1: Manufacturer's Model Structure



Source: Manufacturer's Pharmacoeconomic submission.[3]

Table 7: Data Sources

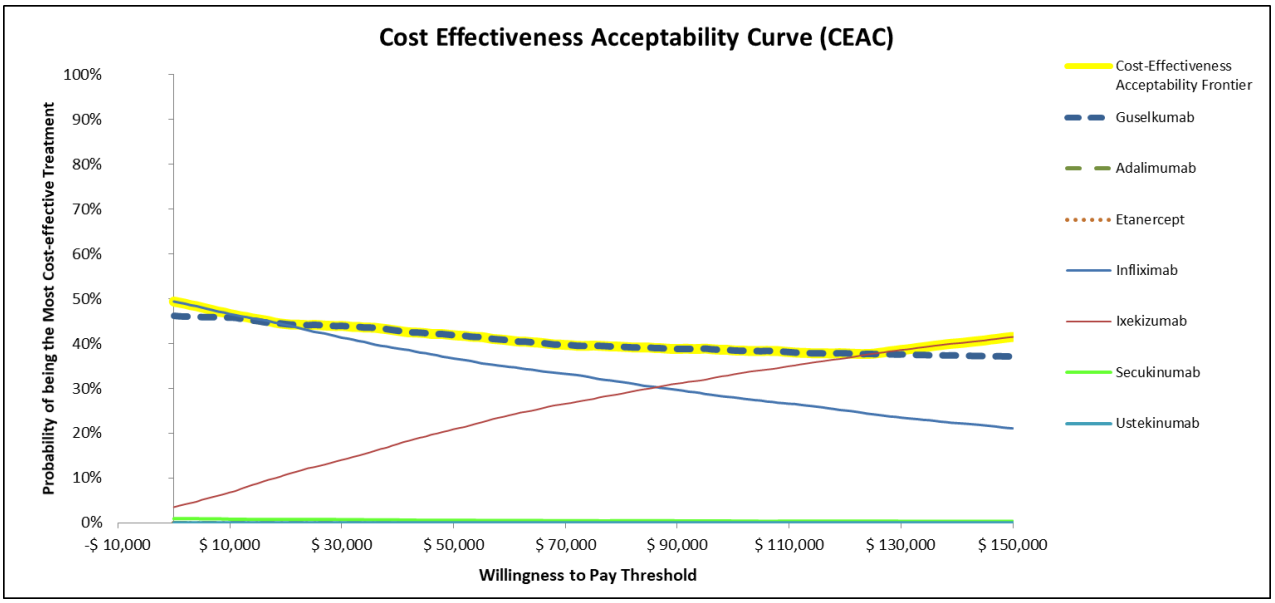
Data Input	Description of Data Source	Comment*
Efficacy, Safety, and Withdrawal		
Efficacy PASI response rates at 12 or 16 weeks	Effects of treatment on the distribution of patients across the PASI response categories were derived from the manufacturer's NMA.	As noted in the CDR's Clinical Review Report, there were a number of concerns with the manufacturer-commissioned NMA which are discussed in the main body of the economic report.
Adverse Events	Serious infection rate was derived from an analysis of the PSOLAR database but excluded guselkumab.	As noted there is a lack of data on the serious infection rate with guselkumab and the assumption that it will be equal to ustekinumab is unproven.
Discontinuation	The probability of discontinuation was derived from an analysis of the PSOLAR Database but excluded guselkumab.	As noted there is a lack of data on discontinuations with guselkumab and the assumption that it will be equal to ustekinumab is unproven.
Natural History		
Mortality	Transition to death was informed by age- and gender-specific all-cause mortality rates for the Canadian general population.	This was appropriate.
Utilities		
Health State Utilities	A common baseline utility was applied to all treatments and was derived from a NICE technology appraisal (NICE 2015). As a common baseline was applied the choice of baseline did not affect the incremental results. The increments by PASI score were informed by a systematic review which identified two studies providing six alternative estimates (Pickford 2017, NICE 2017). The model adopted values derived from an analysis of clinical trial data applying the EQ-PSO instrument.	The chosen method for the increments associated with PASI response likely favoured guselkumab.
Disutilities Due to Serious Infection	Derived from a published study by Tolley.[20]	Appropriate.
Resource Use and Costs		
Costs	All costs appeared to be derived from appropriate sources.	Existing price reductions for comparators were unknown.

CDR = CADTH Common Drug Review; EQ-PSO = EuroQol 5 Dimension Psoriasis Bolt-On; NICE = National Institute for Health and Care Excellence; PASI = Psoriasis Area and Severity Index; PSOLAR = Psoriasis Longitudinal Assessment and Registry.

Cost-Effectiveness Acceptability Curves

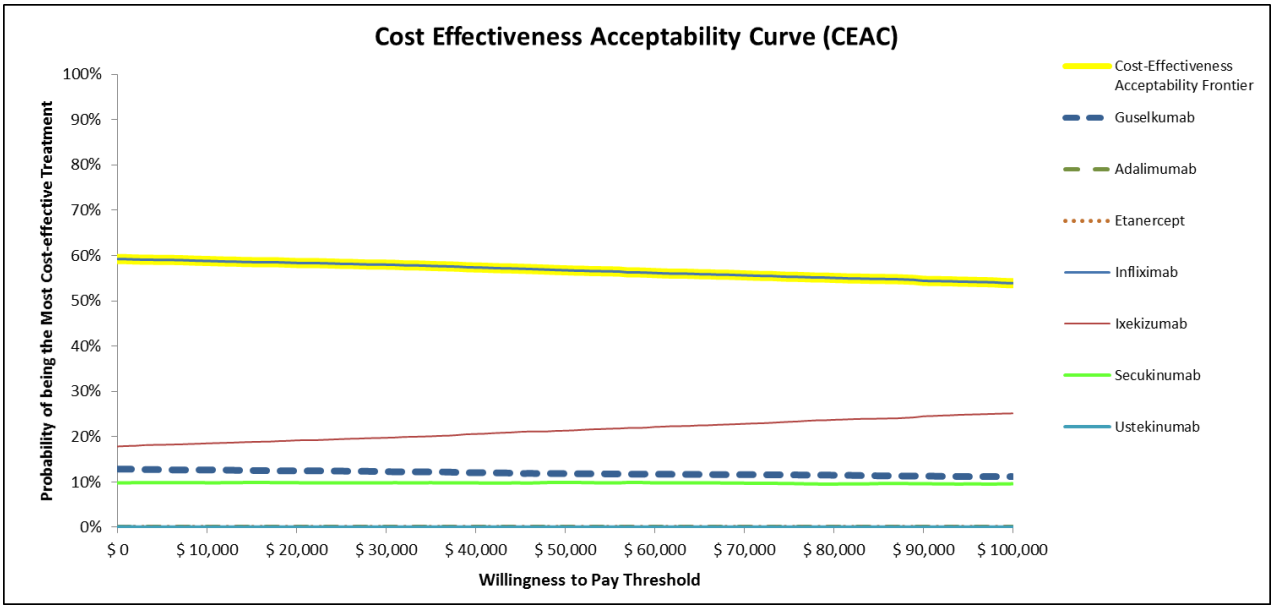
Based on Manufacturer's Economic Model.

Figure 2: Manufacturer's CEAC



Source: Manufacturer's Pharmacoeconomic submission.[3]

Figure 3: CEAC based on CDR Base Case



Manufacturer's Base Case

Table 8: Manufacturer's Base Case – Summary of Mean Costs

Health State	Guselkumab	Adalimumab	Etanercept	Infliximab	Ixekizumab	Secukinumab	Ustekinumab
Drug Costs							
First-Line	$ 135,365	$ 63,720	$ 67,828	$ 88,368	$ 137,927	$ 123,893	$ 94,454
Second-Line	$ 22,032	$ 49,931	$ 49,938	$ 38,844	$ 21,757	$ 26,314	$ 36,890
Third-Line	$ 13,277	$ 31,282	$ 31,716	$ 23,829	$ 13,125	$ 16,253	$ 23,518
BSC	$ 23,257	$ 59,207	$ 61,939	$ 43,221	$ 23,143	$ 30,196	$ 46,583
Total	**$ 193,931**	**$ 204,141**	**$ 211,421**	**$ 194,262**	**$ 195,952**	**$ 196,657**	**$ 201,445**
Resource Use Costs							
First-Line	$ 2,363	$ 1,189	$ 1,171	$ 1,813	$ 2,397	$ 2,186	$ 1,697
Second-Line	$ 411	$ 920	$ 918	$ 721	$ 406	$ 488	$ 678
Third-Line	$ 252	$ 588	$ 594	$ 451	$ 249	$ 307	$ 441
BSC	$ 500	$ 1,274	$ 1,332	$ 930	$ 498	$ 649	$ 1,002
Total	**$ 3,527**	**$ 3,971**	**$ 4,016**	**$ 3,914**	**$ 3,551**	**$ 3,631**	**$ 3,817**
Adverse Event Costs							
First-Line	$ 527	$ 582	$ 417	$ 1,091	$ 528	$ 478	$ 360
Second-Line	$ 139	$ 317	$ 318	$ 246	$ 137	$ 166	$ 235
Third-Line	$ 83	$ 196	$ 199	$ 149	$ 82	$ 102	$ 148
BSC	$ 125	$ 318	$ 332	$ 232	$ 124	$ 162	$ 250
Total	**$ 874**	**$ 1,414**	**$ 1,267**	**$ 1,718**	**$ 872**	**$ 909**	**$ 993**
Total Costs	**$ 198,332**	**$ 209,526**	**$ 216,703**	**$ 199,893**	**$ 200,374**	**$ 201,196**	**$ 206,255**

Source: From manufacturer's economic model.

Price Reduction Analyses

Table 9: Price Reduction for Guselkumab — Based on CDR Base Case

	Vs. Infliximab			Vs. Ixekizumab		
	Incremental Costs ($)	Incremental QALYs	ICER ($/QALY)	Incremental Costs ($)	Incremental QALYs	ICER ($/QALY)
Guselkumab (submitted price)	$5,625	0.004	$1.6 million	$361	–0.020	Ixekizumab dominates guselkumab
5% reduction	$1,533	0.004	$175,112	–$4,650	–0.020	$226,955*
10% reduction	–$4,399	0.004	Guselkumab dominates infliximab	–$9,662	–0.020	$471,550*

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-years.
Note: ICER for ixekizumab v guselkumab as ixekizumab is more effective

Table 10: Price Reduction for Comparators — Based on CDR Base Case

	ICER for Guselkumab Vs. Comparator			
	Submitted Prices	5% Reduction in Comparator Price	10% Reduction in Comparator Price	20% Reduction in Comparator Price
Adalimumab	Guselkumab dominates	Guselkumab dominates	$28,251	$187,743
Etanercept	Guselkumab dominates	Guselkumab dominates	Guselkumab dominates	Guselkumab dominates
Infliximab	$1.6 million	$2.9 million	$4.2 million	$6.9 million
Ixekizumab	Ixekizumab dominates	Ixekizumab dominates	Ixekizumab dominates	Ixekizumab dominates
Secukinumab	$538,944*	Secukinumab dominates	Secukinumab dominates	Secukinumab dominates
Ustekinumab	Guselkumab dominates	Guselkumab dominates	$103,930	$352,212

ICER = incremental cost-effectiveness ratio.
Note: ICER for secukinumab versus guselkumab as secukinumab is more effective

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