Common Drug Review
Pharmacoeconomic Review Report

May 2016

Drug	adalimumab (Humira)
Indication	For the treatment of active moderate to severe hidradenitis suppurativa (HS) in adult patients, who have not responded to conventional therapy (including systemic antibiotics)
Listing request	For the treatment of adult patients with active moderate to severe HS who: • Have a total abscess and nodule count of 3 or greater • Have lesions in at least two distinct anatomic areas, one of which must be Hurley stage II or III Have had an inadequate response to a 90-day trial of oral antibiotics
Dosage form(s)	40 mg pre-filled syringe/pen 40 mg single-use vial
NOC date	31/12/2015
Manufacturer	AbbVie Corporation

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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ABBREVIATIONS

AN	abscess and inflammatory nodule
CDR	CADTH Common Drug Review
EQ-5D	EuroQol Five-Dimensions Health-Related Quality of Life Questionnaire
HS	hidradenitis suppurativa
QALY	quality-adjusted life-year
SC	supportive care

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	**Adalimumab (Humira)**
Study Question	What is the cost-effectiveness of adalimumab + SC versus SC alone for adult patients with active moderate to severe HS who have not responded to conventional therapy (including systemic antibiotics)?
Type of Economic Evaluation	Cost-utility analysis
Target Population	The requested listing criteria represent the population included in the pivotal PIONEER I and II trials, which is the population assessed by the economic analysis and aligned with the Health Canada indication: Adult patients with active moderate to severe HS who: • Have a total abscess and nodule count of 3 or greater • Have lesions in at least 2 distinct anatomic areas, one of which must be Hurley stage II or III • Have had an inadequate response to a 90-day trial of oral antibiotics.
Treatment	Adalimumab
Outcome	QALYs
Comparator(s)	SC alone (from PIONEER I and II trials: topical therapies, antiseptic washes, wound care dressings, oral antibiotics, analgesics, intralesional corticosteroid injections, and incision and drainage procedures)
Perspective	Canadian public health care system
Time Horizon	10 years
Results for Base Case (Provided by Manufacturer)	Incremental cost per QALY gained for adalimumab versus SC is $62,794
Key Limitations and CDR Estimate(s)	• Assumptions relating to modelling transition probabilities beyond treatment discontinuation lacked face validity and biased results in favour of adalimumab. Addressing this issue led to an incremental cost per QALY gained of $293,567. • Some assumptions regarding costs appear to bias the results in favour of adalimumab. Revising resource usage by health state, nursing cost, and compliance rates for adalimumab led to an estimated incremental cost per QALY gained of $80,501. • To address concerns with model design, a CDR reanalysis over a 36-week time horizon and using the utility gains from the clinical trials led to an incremental cost per QALY gained of $356,855. • Assumptions relating to treatment discontinuation in terms of frequency of assessment of response and rules for discontinuation appeared to favour adalimumab. Analysis based on a 36-week time horizon and the modelled utility values provided an incremental cost per QALY gained of $353,817. • Combining the above analyses led to a revised CDR best estimate of $377,516 per QALY gained. With this scenario, a 90% price reduction for adalimumab is needed for an incremental cost per QALY of $40,297. However, analyses by CDR were unable to address a major error in the model, which limits the applicability of assessing the cost-effectiveness of adalimumab in HS.

CDR = CADTH Common Drug Review; HS = hidradenitis suppurativa; QALY = quality-adjusted life-year; SC = supportive care.

EXECUTIVE SUMMARY

Background

Adalimumab (Humira) is a tumour necrosis factor alpha antibody indicated for treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, adult psoriatic arthritis, active ankylosing spondylitis, Crohn disease, psoriasis, ulcerative colitis, and hidradenitis suppurativa (HS).[1] The CADTH Common Drug Review (CDR) completed reviews of adalimumab, and the Canadian Drug Expert Committee issued final recommendations for all indications with the exception of ulcerative colitis (currently under review) and hidradenitis suppurativa.

For HS, the Health Canada Notice of Compliance was issued December 31, 2015, for the treatment of adults with active moderate to severe HS who have not responded to conventional therapy, including systemic antibiotics.

The manufacturer has requested the following listing for adalimumab, for the treatment of adult patients with active moderate to severe HS who:

- Have a total abscess and nodule count of 3 or greater
- Have lesions in at least two distinct anatomical areas, one of which must be Hurley stage II or III
- Have had an inadequate response to a 90-day trial of oral antibiotics.

This patient population reflects the population in PIONEER I and II clinical trials.[2,3]

Adalimumab is available as a 40 mg/0.8 mL syringe for subcutaneous injection at a unit price of $740.36 per syringe.[1,4] At the recommended dose of 160 mg initially at week 0 (administered as four injections in one day or as two injections per day for two consecutive days), followed by 80 mg at week 2 (administered as two 40 mg injections in one day), then 40 mg at week 4, and 40 mg weekly thereafter. At week 12 after the initial dose, for patients without any benefit, discontinuation of treatment should be considered.[1]

The manufacturer submitted a cost-utility analysis to assess the cost-effectiveness of adalimumab plus supportive care (SC) compared with SC alone (which includes topical therapies, antiseptic washes, wound care dressings, oral antibiotics, analgesics, intralesional corticosteroid injections, and incision and drainage procedures)[2,3] in adults with moderate to severe HS who have had inadequate response to conventional systemic HS therapies (including systemic antibiotics). The analysis is based on a Markov model estimating long-term health care costs and quality-adjusted life-years (QALYs) over a 10-year time horizon, from the perspective of the Canadian public health care payer.[5] Health states were based on response, defined as a percentage reduction in abscess and inflammatory nodule (AN) count, using pooled data from the PIONEER I and II clinical trials.[2,3]

The manufacturer reported that adalimumab was associated with greater QALYs and higher costs than SC, with an estimated incremental cost per QALY gained of $62,794.[5]

Summary of Identified Limitations and Key Results

CDR identified a number of limitations with the model submitted by the manufacturer.

Assumptions relating to modelling beyond treatment discontinuation lacked face validity (biased assumptions relating to transition probabilities after discontinuation of therapy), and led to the majority

of the modelled QALY benefit for adalimumab versus SC arising after discontinuation. To address this issue, CDR assumed an equal distribution across health states for both patients who discontinue adalimumab and those on SC. This analysis found an incremental cost per QALY gained of $293,567.

Assumptions concerning costs appeared to bias the results in favour of adalimumab (underestimated nursing costs, uncertain resource use by health state, and lower than 100% compliance rates for adalimumab). Revising the model to include more appropriate assumptions regarding costs lead to an estimated incremental cost per QALY gained of $80,501.

Assumptions related to treatment discontinuation appeared to be inappropriate: assessment of response was judged to be too frequent, and rules for discontinuation of adalimumab too severe. Analysis based on a 36-week time horizon and the modelled utility values can provide some insight into the effect of assuming discontinuation for partial responders. Under this assumption, the incremental cost per QALY gained was $353,817.

The final limitation is a major error within the model: the descriptions of health states were based on an individual's health state relative to his or her previous health rather than his or her absolute health status and are therefore inappropriate for modelling. Given that patients would have a range of very different baseline health states, patients within a given state within the Markov model may have very different symptoms. This precludes the model from being applicable to assess the cost-effectiveness of adalimumab in HS. However, to partially address this concern, a CDR reanalysis was conducted with a 36-week time horizon and using the utility gains from the clinical report. This led to an incremental cost per QALY gained of $356,855.

Based on the limitations cited above, a revised CDR best estimate was obtained, employing revised resource use estimates, with a 36-week time horizon, and the trial-based utility gains. In this analysis, adalimumab was found to be more effective and more costly, with an incremental cost per QALY gained of $377,516.

Based on the manufacturer's base case and on the revised CDR best estimate, reanalysis was conducted assuming alternative prices for adalimumab. Assuming an 80% price reduction, the manufacturer's base case suggested an incremental cost per QALY gained of $43. However, the CDR reanalysis suggested an incremental cost per QALY gained of $77,766. The CDR reanalysis also showed that a 90% price reduction resulted in an incremental cost per QALY gained of $40,297.

Conclusions

The manufacturer's analysis suggested that adalimumab is both more effective, in terms of QALYs, and more costly than SC, with an incremental cost per QALY gained of $62,794. CDR identified multiple limitations favouring adalimumab. Testing these limitations led to a CDR best-estimate incremental cost per QALY of $377,516. Using this scenario, a 90% price reduction for adalimumab is needed for an incremental cost per QALY of $40,297. However, a major error in terms of data applicability in the model, which cannot be corrected by CDR, precludes using the model, rendering it inappropriate for assessing the cost-effectiveness of adalimumab in HS.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer's submission is based on a Markov model with five health states (Figure 1).

1. *High response:* defined as a reduction of at least 75% in total abscess and inflammatory nodule (AN) count, with no increase in abscesses or draining fistulas from baseline
2. *Response:* defined as a reduction of at least 50% but less than 75% in AN, with no increase in abscesses or draining fistulas from baseline
3. *Partial response:* defined as a reduction of at least 25% but less than 50% in AN, with no increase in abscesses or draining fistulas from baseline; or a reduction of at least 25% in AN, but with an increase in abscesses and/or AN reduction
4. *Non-response:* defined as a reduction of less than 25% in AN count
5. Death.

The first two cycles of the model had a length of two weeks, with subsequent cycles of four weeks' duration. Model time horizon was 10 years.[5] Patients entered the model in the non-response health state; although patients within the clinical trials would have a range of different AN counts, the manufacturer suggested that patients entering the model would reflect those entering the PIONEER I and II trials.[2,3] Transition probabilities were based on clinical trial data from PIONEER I and II.[2,3] At the end of 12 weeks (induction), non-responders on adalimumab would be assumed to discontinue treatment. Subsequently, every four weeks, patients who entered the non-response state were assumed to discontinue treatment. At the end of 36 weeks, patients in the partial response state were also assumed to discontinue treatment, and, in every subsequent four weeks, patients entering this state would discontinue. Discontinuers were not assumed to have the same outcomes as patients on supportive care (SC). The modelled transition probabilities after trials (from 36 weeks) were extrapolated using the week 12 to 36 data from the PIONEER clinical trials for the base case; a "last health state carried forward" extrapolation method was explored in the sensitivity analysis.[5]

Utility values were derived from the PIONEER II clinical trial using the EuroQol Five-Dimensions Health-Related Quality of Life Questionnaire (EQ-5D) utility instrument.[3,6] Utility values ranged from [redacted] for non-response to [redacted] for high response, a difference of [redacted] Thus, five years in the non-response state was assumed to be equivalent to three years in the high-response state, implying that patients in the non-response state would be willing to trade 40% of their existing life expectancy to be in the high-response state.

Costs for treatments included only the cost of adalimumab, based on a cost of $740.36 for a 40 mg dose,[4] an annual cost of maintenance of $19,249 (without markup). Costs were adjusted down by assuming lack of compliance: compliance rates of [redacted] in the induction phase and [redacted] in the maintenance phase, taken from PIONEER clinical trials.[2,3] SC costs were excluded, as they were assumed to be similar for the compared cohorts, adalimumab plus SC and SC alone, which is likely a conservative assumption against adalimumab considering that patients on adalimumab would be likely to receive less SC therapy. Education costs for adalimumab were based on three one-hour sessions with a nurse at a cost of $37.14. This, however, excludes benefits paid to the nurse and overheads; it therefore should be higher.[7]

Resource use was provided by health state and was obtained from an unpublished survey of UK health care practitioners conducted by the manufacturer. Total annual medical costs were estimated to be $2,662 for high responders, $2,266 for responders, $2,038 for partial responders, and $5,561 for non-responders.[5] The analysis also assumed adverse event rates taken from PIONEER I and II,[2,3] costed based on assumptions for resource use.[5]

The analysis was presented in terms of incremental cost per quality-adjusted life-year (QALY) gained. A modest range of sensitivity analyses were conducted relating to time horizon, clinical trial source, extrapolation and imputation methods, discontinuation rates, costs per health state, and utility values. Probabilistic sensitivity analysis was conducted.[5]

2. MANUFACTURER'S BASE CASE

The manufacturer's analysis estimated, over a 10-year time horizon, a QALY gain with adalimumab versus SC of 0.287, with incremental costs of $18,005. This leads to an estimated incremental cost per QALY gained of $62,794.

TABLE 2: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE CASE

	Total Costs ($)	Incremental Cost of Adalimumab ($)	Total QALYs	Incremental QALYs of Adalimumab	Incremental Cost per QALY
Supportive care	$39,783		4.039		
Adalimumab	$57,788	$18,005	4.326	0.287	$62,794

QALY = quality-adjusted life-year.
Source: Adapted from the manufacturer's pharmacoeconomic submission.[5]

3. SUMMARY OF MANUFACTURER'S SENSITIVITY ANALYSES

A range of sensitivity analyses were included. Analyses with a significant impact on results are as follows:[5]

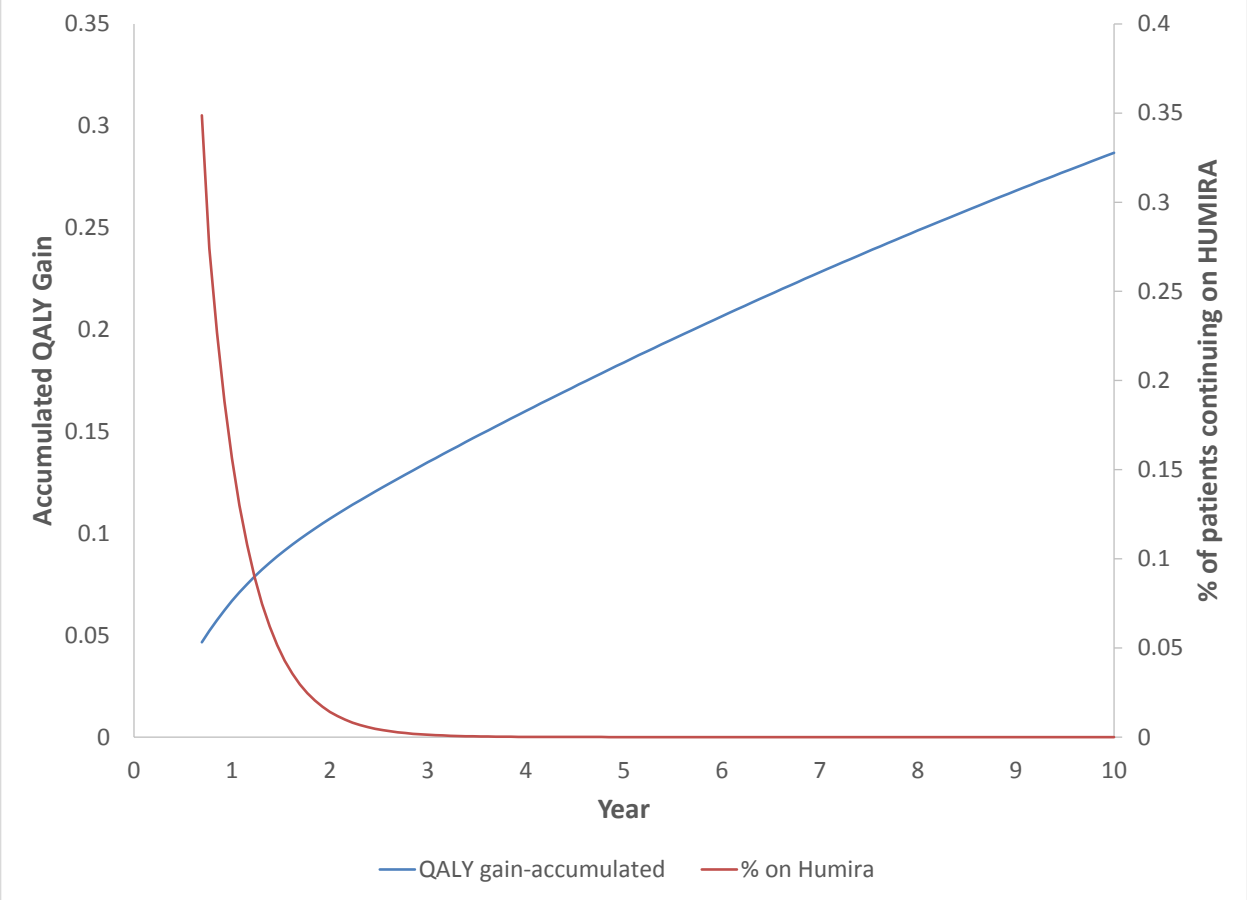
- Time horizon: assuming a time horizon of five years led an incremental cost per QALY gained of $107,470. The higher incremental cost per QALY gained is primarily due to fewer incremental QALYs: 0.184 versus 0.287. Note that only 0.001% of patients are assumed to still be on adalimumab at five years, so the incremental QALYs gained between five and 10 years occurs despite the fact that no patients would be receiving adalimumab.
- In the base-case analysis, maintenance data for adalimumab and SC come from different trials, thus not representing the original randomization. Analysis based on using evidence for both treatments from the same trial led to higher estimates of incremental cost per QALY gained: $76,413 to $77,924.
- Analysis assuming that patients who discontinue treatment will continue in the health state at the last follow-up provided a higher estimate of incremental cost per QALY gained of $172,703.
- Varying utility values: utility values applied to response health states were varied independently using their 95% confidence intervals (CIs). Varying the utility score for the non-response health state resulted in an incremental cost per QALY gained of between $47,058 and $94,345 (range covering the resulting values for all other health states varied independently). Additionally, a further analysis in which utility values were derived using changes in EQ-5D relative to baseline from the clinical trial (PIONEER II) led to an incremental cost per QALY gained of $113,613.

The manufacturer's probabilistic sensitivity analysis found the probability that adalimumab was cost-effective was 79.5%, assuming a willingness-to-pay for a QALY threshold of $100,000; 61.8% assuming a threshold of $75,000; and 27.5% assuming a threshold of $50,000.[5]

4. LIMITATIONS OF MANUFACTURER'S SUBMISSION

Long-term outcomes: The manufacturer's submission assumes that patients who discontinue adalimumab will have different long-term outcomes than those on SC. This is illustrated convincingly in Figure 1. By comparing accumulated QALY gains at each time point with the percentage of patients still on adalimumab, it is evident that much of the estimated QALY gains occur after therapy has been discontinued. For example, at two years, only 1.4% of adalimumab patients are assumed to be on therapy, and the QALY gains at two years compared with SC are 0.108. At 10 years, the QALY gains are 0.287. Thus, 62% of the QALY gains occur after 98.6% of patients discontinue adalimumab. This suggests the analysis is clearly erroneous.

FIGURE 1: ACCUMULATED QALY GAINS OVER 10 YEARS IN COMPARISON WITH THE PERCENTAGE OF PATIENTS STILL ON ADALIMUMAB



QALY = quality-adjusted life-year.

Resource use: The manufacturer's submission had a number of limitations relating to resource use. It assumed differential resource use by health state. Although this may be possible, the method of estimation is weak and inappropriate. The manufacturer assumed lower than 100% compliance and underestimated the cost of nursing time.

Discontinuation: The manufacturer assumed that, after 12 weeks, patients would discontinue adalimumab if they were non-responders at each subsequent four-week follow-up. Furthermore, after 36 weeks, patients were assumed to discontinue adalimumab if they were partial responders at each subsequent four-week follow-up.[5] The clinical expert disputed these assumptions. The expert assumed that patients would be assessed every 12 weeks, not every four weeks. Furthermore, the expert assumed that, if patients were previously responsive to treatment but were now non-responders, that they would stay on treatment for another four weeks and try increasing either the dosage or frequency of treatment. Finally, the expert assumed that some patients would be happy with at least a 25% response, and therefore not all partial responders would stop treatment. The assumptions suggested by the clinical expert would make adalimumab look much less cost-effective.

Model design: The final limitation suggests a major flaw with the model design. In a Markov model, health states should reflect the absolute state a patient is in. However, in the manufacturer's model, they are reflective of a relative change from baseline, with patients having different baselines. Thus, patients in the same health state may have quite different absolute health states, and it is feasible that patients in a *lesser* health state in this model may actually have better absolute health. For example, if patient X had much worse disease at entry into the model than patient Y, then if patient Y has a partial response, he or she may have a better absolute health state than patient X has with a full response. To overcome this major flaw within the model, an alternative model design using absolute health states, rather than relative changes, would be required.

5. CADTH COMMON DRUG REVIEW REANALYSES

5.1 CADTH Common Drug Review Reanalyses

5.1.1 Long-Term Outcomes

To address the limitation with respect to different long-term outcomes for adalimumab discontinuers, a reanalysis was conducted in which, for each cycle, those patients who were adalimumab discontinuers were allocated to states assuming the same proportions as those in SC. This approach assumed no difference in outcomes after discontinuation. Under this assumption, the incremental cost per QALY gained was $274,853.

TABLE 3: CDR REANALYSIS ASSUMING THE SAME DISTRIBUTION FOR ADALIMUMAB DISCONTINUERS AS SC

	Adalimumab	SC	Adalimumab versus SC
Costs (2015$)			
Treatment costs	$22,490	$0	$22,490
Administration costs	$111	$0	$111
Direct medical costs	$38,240	$39,104	–$864
Total costs	$61,402	$39,783	$21,619
Effectiveness			
QALYs	4.118	4.039	0.079
Incremental cost per QALY gained			$274,853

CDR = CADTH Common Drug Review; QALY = quality-adjusted life-year; SC = supportive care.

5.1.2 Resource Use

CDR reanalysis adopted revised assumptions relating to resource use. Nursing costs were increased to include employee benefits (costed at 25% of salary), although overhead costs were not included, 100% compliance with drug was assumed for costs, resource use was assumed to be the same for each state as the partial response state, and adverse event costs were assumed to be the same. Under these assumptions, the incremental cost per QALY gained was $80,501.

TABLE 4: CDR REANALYSIS USING ALTERNATIVE RESOURCE USE AND COSTS ASSUMPTIONS

	Adalimumab	SC	Adalimumab versus SC
Costs (2015$)			
Treatment costs	$22,943	$0	$22,943
Administration costs	$139	$0	$139
Direct medical costs	$16,070	$16,070	–$0
Total costs	$39,831	$16,749	$23,082
Effectiveness			
QALYs	4.326	4.039	0.287
Incremental cost per QALY gained			$80,501

CDR = CADTH Common Drug Review; QALY = quality-adjusted life-year; SC = supportive care.

5.1.3 Discontinuation

It was not possible to reprogram the model based on the clinician's suggested alternative assumptions relating to discontinuation. Nevertheless, if it were assumed that a proportion of partial responders remained on treatment, instead of assuming that patients who are partial responders would discontinue therapy, then adalimumab would be less cost-effective. Additionally, if it were assumed that response was assessed less frequently and dosage or frequency of adalimumab was increased if patients were non-responders, rather than assuming that patients would be assessed for non-response every four weeks and would discontinue if found to be non-responders, then adalimumab would be less cost-effective. Analysis based on a 36-week time horizon and the modelled utility values may provide some insight into the effect of assuming discontinuation for partial responders. Under this assumption, the incremental cost per QALY gained was $353,817.

TABLE 5: CDR REANALYSIS USING 36-WEEK TIME HORIZON AND MODELLED QALY GAINS

	Adalimumab	SC	Adalimumab versus SC
Costs (2015$)			
Treatment costs			
Administration costs	$18,083	$0	$18,083
Direct medical costs	$111	$0	$111
Total costs	$2,626	$3,208	–$582
Effectiveness	$21,380	$3,887	$17,493
QALYs			
Incremental cost per QALY gained	0.439	0.389	0.49

CDR = CADTH Common Drug Review; QALY = quality-adjusted life-year; SC = supportive care.

5.1.4 Model Design

The final limitation relates to the design of the model. This is not readily addressed, but restricting the analysis to a 36-week time horizon and using the utility gains from the clinical report — a utility gain of 0.071, which translates to a 0.049 QALY gain over 36 weeks — provides insights. It should be noted that that only 27.4% of adalimumab patients continue on therapy after 36 weeks. From this analysis, the incremental cost per QALY gained was $356,855, although an alternative assumption relating to the timing of the QALY gains would lead to an ICUR two times larger.

TABLE 6: CDR REANALYSIS USING 36-WEEK TIME HORIZON AND TRIAL UTILITY VALUES

	Adalimumab	SC	Adalimumab versus SC
Costs (2015$)			
Treatment costs	$18,083	$0	$18,083
Administration costs	$111	$0	$111
Direct medical costs	$2,626	$3,208	–$582
Total costs	$21,380	$3,887	$17,493
Effectiveness			
QALYs			0.049
Incremental cost per QALY gained			$356,855

CDR = CADTH Common Drug Review; QALY = quality-adjusted life-year; SC = supportive care.

5.1.5 CADTH Common Drug Review Best Estimate

To address concerns about long-term outcomes, resource use, utilities, and discontinuations (A through D), the CDR best estimate employed the revised resource use estimates from above, with a 36-week time horizon and the trial-based utility gains. Under this scenario, the incremental cost per QALY gained was $377,516.

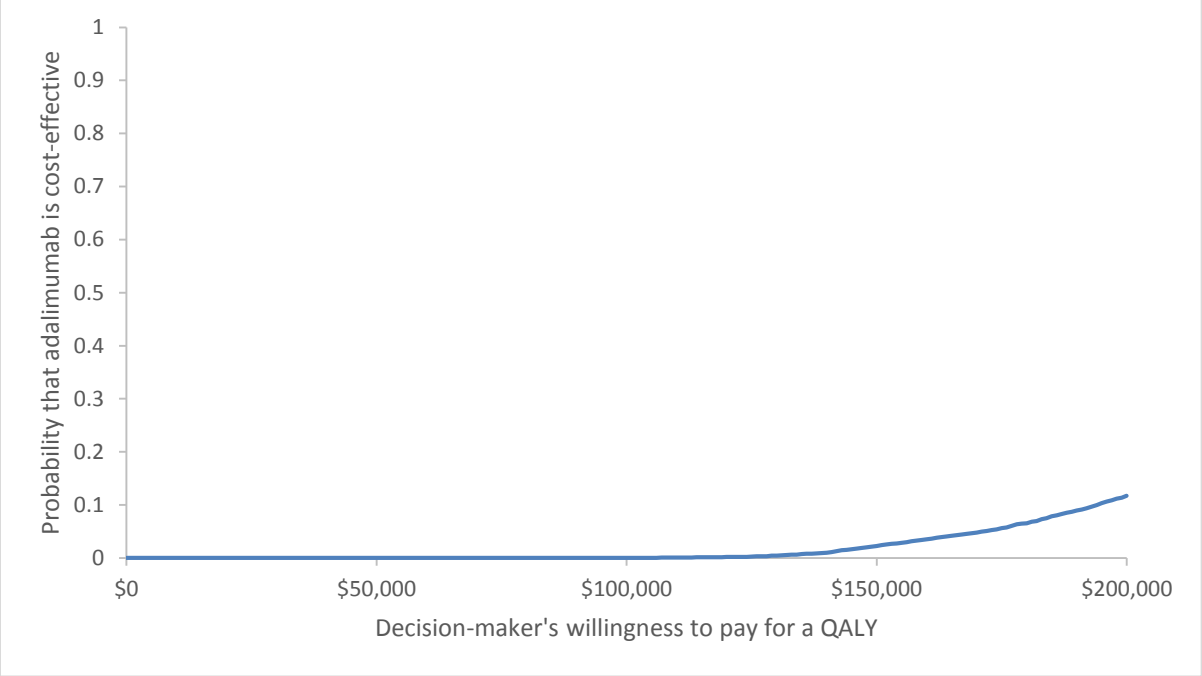
TABLE 7: SUMMARY OF RESULTS OF THE CDR BEST ESTIMATE

	Adalimumab	SC	Adalimumab versus SC
Costs (2015$)			
Treatment costs	$18,471	$0	$18,471
Administration costs	$139	$0	$139
Direct medical costs	$1,463	$1,463	$0
Total costs	$20,699	$2,142	$18,556
Effectiveness			
QALYs			0.049
Incremental cost per QALY gained			$377,516

CDR = CADTH Common Drug Review; QALY = quality-adjusted life-year; SC = supportive care.

A probabilistic sensitivity analysis was conducted based on the CDR reanalysis (Figure 2). The analysis found there was 0% probability of adalimumab being cost-effective at values less than $97,000. At $200,000, the probability of adalimumab being cost-effective was 11.8%.

FIGURE 2: PROBABILISTIC SENSITIVITY ANALYSIS ON THE CADTH COMMON DRUG REVIEW REANALYSIS



QALY = quality-adjusted life-year.

5.1.6 Price-Reduction Scenarios

The reanalysis was conducted assuming alternative prices for adalimumab. Assuming an 80% price reduction, the manufacturer's model suggested an incremental cost per QALY gained of $43. However, the CDR reanalysis would suggest an incremental cost per QALY gained of $77,766.

TABLE 8: CDR REANALYSIS PRICE-REDUCTION SCENARIOS

ICURs of Submitted Drug Versus Comparator		
Price	**Base-case analysis submitted by manufacturer**	**CDR best estimate**
Submitted	$62,794	$377,516
10% reduction	$54,951	$340,048
20% reduction	$47,107	$302,579
30% reduction	$39,263	$265,110
40% reduction	$31,419	$227,641
50% reduction	$23,575	$190,173
60% reduction	$15,731	$152,704
70% reduction	$7,887	$115,235
80% reduction	$43	$77,766
90% reduction	Dominant	$40,297

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio.

6. ISSUES FOR CONSIDERATION

The analysis is restricted to patients with moderate and severe disease. Use by patients with less severe disease would likely be less cost-effective than the indication covered in this review.

7. PATIENT INPUT

Two patient groups, the Canadian Skin Patient Alliance and Hidradenitis Suppurativa (HS) Aware, submitted input for this submission. Pain is one of the primary concerns associated with HS, with most patients finding it to be the hardest part of the disease not only to control but to deal with on a daily basis. Patients often experience restricted mobility that can further impede everyday activities. Problems with sleep and fatigue and psychological impacts of the disease are common; many patients become depressed.

Many patients note the intense time constraints, social constraints, and financial hardship associated with both wound care and systemic treatments. The financial burden and isolation are also further compounded by many patients' inability to maintain employment.

As patients have few treatment options (adalimumab is the only currently approved treatment for HS), there is an expectation that adalimumab could potentially have a positive impact. Patients voiced some fears regarding the side effects and costs associated with adalimumab. In addition, there is some skepticism associated with its effectiveness.

From a health-economic point of view, we can highlight that patient input emphasized the impact of the disease on patients' quality of life. This component was included in the health economic assessment, being a driver of the results, and having been tested by CDR. For a higher probability that adalimumab will be cost-effective in this population, the cost of treatment should be optimally aligned with its potential positive impact on quality of life. In terms of indirect cost, the manufacturer submitted a scenario including loss of productivity costs for patients with HS. Considering this loss of productivity due to HS increases the cost-effectiveness of adalimumab; however, in the CDR best-estimate case, the incremental cost per QALY gained when including indirect costs was $358,505. However, the indirect

impact on caregivers was not considered by the manufacturer's health-economic analysis, either from a quality of life or an economic point of view.

8. CONCLUSIONS

The manufacturer's analysis suggested that adalimumab is both more effective in terms of QALYs and more costly than SC, with an incremental cost per QALY gained of $62,794. However, CDR identified multiple limitations favouring adalimumab, which relate to the extrapolation of effects after discontinuation, assumptions about resource use, and rates of discontinuation.

Addressing these limitations led to a CDR best-estimate incremental cost per QALY of $377,516. Using this scenario, a 90% price reduction for adalimumab is needed for an incremental cost per QALY of $40,297.

However, the above scenarios are of limited interest because there is a major error in the model that cannot be corrected by CDR and that precludes the model's applicability of assessing the cost-effectiveness of adalimumab in HS, limiting the outputs from this review.

APPENDIX 1: COST COMPARISON

The treatments presented in Table 9 have been deemed by clinical experts to be options for the treatment of active moderate to severe HS. These options were selected informed by the literature[8] and clinical expertise. These may represent, mostly in combination, comparators for adalimumab; however, adalimumab is the only drug indicated for treating HS, and the available evidence for alternatives is highly limited.[8]

TABLE 9: COST-COMPARISON TABLE FOR HIDRADENITIS SUPPURATIVA

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose[a]	Average Annual Drug Cost ($)
Adalimumab (Humira)	40 mg/0.8 mL	Pre-filled syringe or auto-injector	740.3600	160 mg at week 0, 80 mg at week 2, 40 mg at week 4, and 40 mg each week thereafter	Year 1: 39,979 Year 2 and onwards: 38,499
Drugs not indicated					
Other biologics					
Etanercept (Enbrel)	50 mg/mL	Pre-filled syringe or auto-injector	395.3900	50 mg twice weekly	41,121
Infliximab (Remicade)	100 mg/10 mL	Injection	987.5600	5 mg/kg weeks 0, 2, 6, and every 8 weeks thereafter[b]	Year 1: 39,502[b] Year 2 and onwards: 32,096[b]
Ustekinumab (Stelara)	45 mg/0.5 mL 90 mg/mL	Injection	4,593.1400	45 mg (90 mg if patient weight ≥ 100 kg) at weeks 0, 4, 16, and 28 then every 12 weeks thereafter	Year 1: 22,966 Year 2 and onwards: 19,904
Antibiotic therapies					
Dapsone (generic)	100 mg	Tab	1.3391[c]	50 to 200 mg daily	Per month: 20 to 80
Doxycycline (generics)	100 mg	Tab or cap	0.5860[c]	50 to 100 mg twice daily, continuously for at least 3 months then tapered, if possible	Per month: 18 to 36
Minocycline (generics)	50 mg 100 mg	Cap	0.3064[c] 0.5912[c]	50 to 100 mg twice daily	Per month: 18 to 35
Tetracycline (generics)	250 mg	Cap	0.0657	500 mg twice daily	Per month: 8
Clindamycin plus rifampin (generics)	150 mg 300 mg	Cap	0.2217 0.4434	300 mg twice daily plus 600 mg once daily for 10 weeks	10 weeks: 208
	150 mg 300 mg	Cap	0.6633 1.0441		
Conventional immunosuppressants					
Anakinra (Kineret)	100 mg/0.67mL	Pre-filled syringe	47.5800[c]	100 mg SC daily	Per month: 1,427

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose[a]	Average Annual Drug Cost ($)
Cyclosporine (generics)	25 mg 50 mg 100 mg	Cap	0.9952 1.9400 3.8815	3 to 6 mg/kg per day in divided doses for several weeks to months[b]	Per month: 345 to 640
Prednisone (generics)	5 mg 50 mg	Tab	0.0220 0.1735	40 to 60 mg for 3 to 4 days, then tapered over subsequent 10 days	Per course: 1 to 3
Oral retinoids					
Acitretin (Soriatane)	10 mg 25 mg	Cap	2.3573 4.1400	Up to 35 mg daily	860 to 2,372
Isotretinoin (Accutane, Clarus, Epuris)	10 mg 20 mg 30 mg 40 mg	Cap	0.9397 1.4424 1.8139 1.9173	40 to 80 mg daily	700 to 1,400
Hormone therapies					
Oral contraceptives (various)	various	21 or 28 tabs	7.2800 to 23.0790	Female patients only: 1 tab daily or as package directs (1 pkg starting every 28 days)	94 to 300[d]
Dutasteride (generics)	0.5 mg	Cap	0.4205	1 to 10 mg daily	Per month: 25 to 250
Finasteride (generics)	1 mg 5 mg	Tab	1.1455[e] 0.4633	1 to 10 mg daily	Per month: 14 to 137

Cap = capsule; pkg = package; SC = subcutaneous; Tab = tablet.
Note: All prices are from the Ontario Drug Benefit (ODB) Formulary and Exceptional Access Program (both accessed February 2016)[4] unless otherwise indicated and do not include dispensing fees; actual prices reimbursed by plans may be lower than those publically listed or submitted to the CADTH Common Drug Review.
[a] Dosing for adalimumab is from product monograph.[1] Dosing for comparators is from Up-to-Date Treatment of hidradenitis suppurativa (acne inversa), retrieved November 20, 2015[8] with additional input from a clinical expert.
[b] Assumes 95 kg patient, the approximate mean weight of the patients in the PIONEER I trial,[2] with excess medication in vial wasted.
[c] Saskatchewan formulary (February 2016).[9]
[d] Cost range based on lowest (Min-Ovral) and highest (Tri-Cyclen) ODB list prices for reimbursed contraceptives (February 2016).[4]
[e] Ontario wholesale price, Delta PA, IMS Brogan (retrieved February 2016).

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 10: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS ADALIMUMAB RELATIVE TO SUPPORTIVE CARE?

Adalimumab Versus SC	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes	X					
Quality of life	X					
Incremental CE ratio or net benefit calculation	Manufacturer $62,794 per QALY CDR $407,491 per QALY					

CDR = CADTH Common Drug Review; CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 11: 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"*	The model is relatively simple, but it is coded to such an extent to make it difficult to follow without some time commitment. Simplifying of formulas would not change the results but would have been more transparent and facilitate greater reanalysis.		
Was the material included (content) sufficient?	X		
Comments *Reviewer to provide comments if checking "poor"*	None		
Was the submission well organized and was information easy to locate?	X		
Comments *Reviewer to provide comments if checking "poor"*	None		

TABLE 12: AUTHORS' 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 4: REVIEWER WORKSHEETS

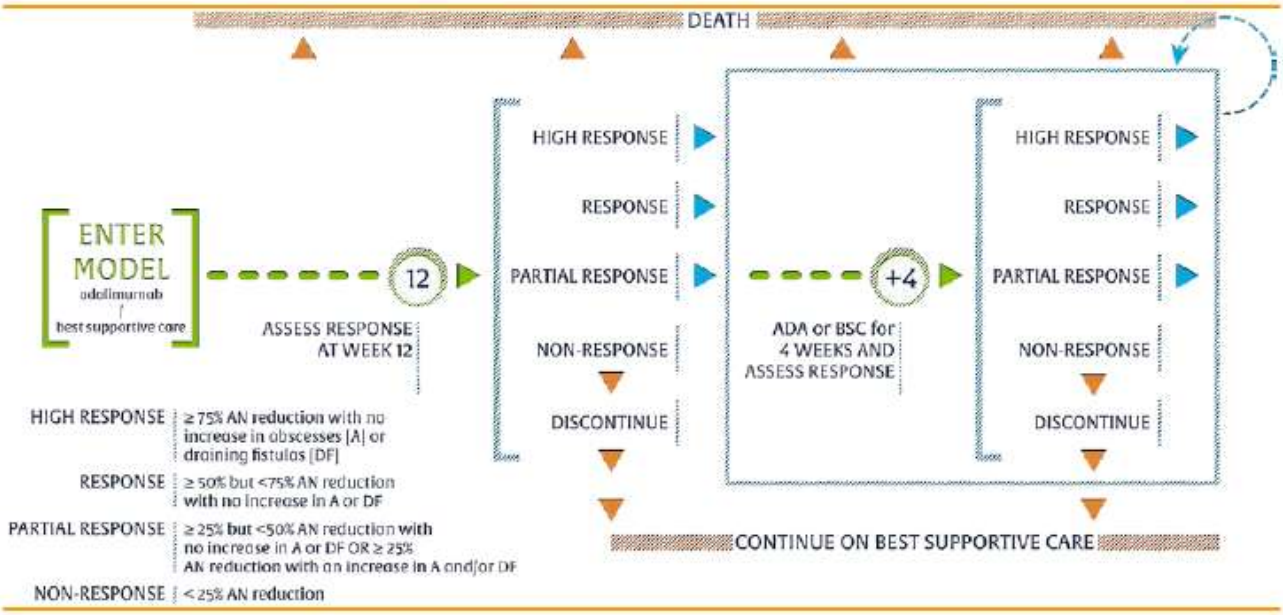
Manufacturer's Model Structure

Model Design

The model is a Markov model with cycle length of two weeks for the first two cycles, and subsequently four weeks up. The base-case analysis has a 10-year time horizon. The Markov model has five health states (Figure 3):

1. *High response:* defined as reduction of at least 75% total abscess and inflammatory nodule (AN) count, with no increase in abscesses or draining fistulas from baseline
2. *Response:* defined as reduction of at least 50% but less than 75% AN, with no increase in abscesses or draining fistulas from baseline
3. *Partial response:* defined as reduction of at least 25% but less than 50% AN, with no increase in abscesses or draining fistulas from baseline; or reduction of at least 25% AN, but with an increase in abscesses and/or AN reduction
4. *Non-response:* defined as reduction of less than 25% in AN count
5. Death.

FIGURE 3: MODEL SCHEMA



ADA: adalimumab (Humira); **AN:** abscess and nodule count; **BSC:** best supportive care (or supportive care); **DF:** draining fistula
Note: After week 12, non-responders were discontinued; patients in high response, response or partial response would discontinue HUMIRA based on a specified rate. After week 36, all partial responders and non-responders will discontinue treatment with HUMIRA.

Source: From the manufacturer's pharmacoeconomic submission.[5]

Model Validation up to 36 Weeks

The manufacturer provides evidence that the model replicates results from the clinical trials up to 36 weeks (Table 12). This is intuitive, given that the model uses data from the clinical trials for the transition probabilities.

TABLE 13: MODELLED TRANSITION PROBABILITY EXTRAPOLATION: VALIDATION AGAINST PHASE 3 CLINICAL TRIALS DURING WEEK 0 TO WEEK 36

	Observed from M11-810 and M11-313				Predicted in the CEA			
Week	High Response %	Response %	Partial Response %	Non-response %	High Response %	Response %	Partial Response %	Non-response %
0	0.0%	0.0%	0.0%	100.0%	0.0%	0.0%	0.0%	100.0%
12	42.6%	33.8%	23.5%	0.0%	44.2%	30.2%	25.6%	0.0%
36	36.8%	20.6%	5.9%	36.8%	36.8%	20.6%	5.9%	36.7%

CEA: cost-effectiveness analysis.
Source: From the manufacturer's pharmacoeconomic submission.[5]

Data Inputs

Data inputs and model assumptions used are summarized in Table 14 and Table 15. Transition probabilities were based on clinical trial data. At the end of 12 weeks (induction), non-responders on adalimumab were assumed to discontinue treatment. Subsequently, every four weeks, patients who entered the non-response state were assumed to discontinue treatment. At the end of 36 weeks, patients in the partial response state were also assumed to discontinue treatment, and, in every subsequent four weeks, patients entering this state would discontinue. Discontinuers were not assumed to have the same outcomes as patients on supportive care (SC).

Utility values were derived from the PIONEER II clinical trial.

Costs for treatments included the cost of adalimumab, based on a cost of $740.36 for a 40 mg dose — an annual cost of maintenance of $19,249. Costs were adjusted down by assuming lack of compliance. Supportive care costs were excluded, as they were assumed to be similar for both SC and adalimumab. Education costs for adalimumab were based on three one-hour sessions with a nurse. Resource use was provided by health state and was obtained from a survey of health care practitioners. The analysis also assumed higher adverse event costs for SC than for adalimumab.

Indirect costs were considered in a scenario analysis. The indirect costs were estimated based on weekly earnings per patient and overall work impairment experienced by hidradenitis suppurativa (HS) patients (estimated probabilities per health state based on the Work Productivity and Activity Impairment Questionnaires collected in PIONEER I and II). Average weekly earnings per patient were estimated based on the percentages of male and female patients specified in the model (from PIONEER I and II), gender-specific employment rates, and the weekly earning per employee obtained from Statistics Canada.[5]

TABLE 14: DATA SOURCES

Data Input	Description of Data Source	Comment
Transition probabilities	Transition probabilities during the first 36 weeks (the trial periods) were derived from PIONEER I and II.[2,3] Beyond the trial period (after 36 weeks), the transition probabilities from the trials were extrapolated by applying patterns similar to those in the first 36 weeks. An alternative extrapolation method was explored in the sensitivity analysis: the last health state carried forward extrapolation method.	Appropriate up to 36 weeks Questionable and uncertain after 36 weeks
Utilities	From EQ-5D data collected during the PIONEER II trial.[3] These data were not collected during PIONEER I.[2]	Source appropriate; however, the validity of the utility values may be questioned
Adalimumab treatment cost	The unit cost of adalimumab was obtained from the Ontario Drug Benefit Formulary.[4]	Appropriate
Compliance rates for adalimumab	Based on the observed compliance rates of patients treated with adalimumab in PIONEER I and II[2,3]	Questionable in term of its generalization to real life
Education cost for adalimumab administration	The model included the cost to educate patients to self-inject adalimumab at the beginning of treatment. It was assumed that 3 1-hour sessions with a nurse were required to educate patients. The cost of 1-hour face-to-face meeting with a nurse (general practice) was obtained from the Ontario nurses' collective agreement.[7]	Appropriate; however, the costs associated with employee benefits and overheads were excluded
Resource use	The model assumed that resource use was dependent on health state. Resource use by health states was estimated based on inputs from a survey of Canadian dermatologists and surgeons (plastic and general). The physicians were surveyed regarding the frequency of each type of resource use, stratified by health state. The information was collected for patients with moderate and severe HS, separately, and weighted based on the proportions of patients in each disease severity category, as observed in PIONEER I and II.[2,3]	The method of estimation of resource use is weak and associated with uncertainty
Unit costs for resource use components	The unit costs of each type of resource use were obtained from different sources, using Ontario costs as a proxy for Canada. Where appropriate, costs were inflated to 2015 $CAN.	Appropriate
Indirect costs (weekly)	Overall work impairment by health state was estimated based on the Work Productivity and Activity Impairment Questionnaires collected in PIONEER I and II.[2,3] Earnings per employee were obtained from Statistics Canada.[10,11]	The generalization of these trial data to the Canadian perspective is highly questionable

EQ-5D = EuroQol Five-Dimensions Health-Related Quality of Life Questionnaire; HS = hidradenitis suppurativa.

TABLE 15: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
Nursing administration costs excludes benefits	Inappropriate Inclusion of benefits is necessary.
Costs of adalimumab were adjusted down by assuming lack of compliance	Inappropriate
Differences in resource use by response were assumed through physician survey	Not validated If data on resource use based on response from real-world data were appropriate, this could be included in the analysis.
Health states based on relative response, not absolute health status	Inappropriate
The manufacturer assumed that, after 12 weeks, patients would discontinue adalimumab if they were non-responders at each subsequent 4-week follow-up. Furthermore, after 36 weeks, patients were assumed to discontinue adalimumab if they were partial responders at each subsequent 4-week follow-up	Inappropriate The clinical expert disputed these assumptions. The expert would assume that patients would be assessed every 12 weeks, not every 4 weeks. The expert would assume that, if patients were previously responsive to treatment but were now non-responders, they would stay on treatment for another 4 weeks and try increasing either the dosage or frequency of treatment. Finally, the expert would assume that some patients would be happy with at least a 25% response and therefore not all partial responders would stop treatment.
Utility values for the health states were obtained from the clinical trials	The validity of the utility values needs to be considered.
Benefit from adalimumab continued long after treatment discontinuation	Highly inappropriate. Leads to high degree of bias in manufacturer's results.

Manufacturer's Results

In its base case, the manufacturer reported an incremental cost per QALY gained of $62,794 for adalimumab versus SC (Table 16).

TABLE 16: MANUFACTURER BASE-CASE RESULTS

	Adalimumab	SC	Adalimumab versus SC
Discounted costs (2015$)			
Treatment costs	$22,490	$0	$$22,490
Administration costs	$111	$0	$111
Surgery-related medical costs	$32,794	$37,165	–$4,371
Non–surgery-related medical costs	$1,832	$1,939	–$107
Adverse event costs	$561	$679	–$119
Total costs	$57,788	$39,783	$18,005
Discounted effectiveness			
QALYs	4.326	4.039	0.287
Incremental cost per QALY gained			$62,794

QALY = quality-adjusted life year; SC = supportive care.
Source: From the manufacturer's pharmacoeconomic submission.[5]

When considering a societal perspective for the manufacturer's base case, it resulted in an incremental cost per QALY gained of $45,426 for adalimumab versus SC.[5]

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