Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

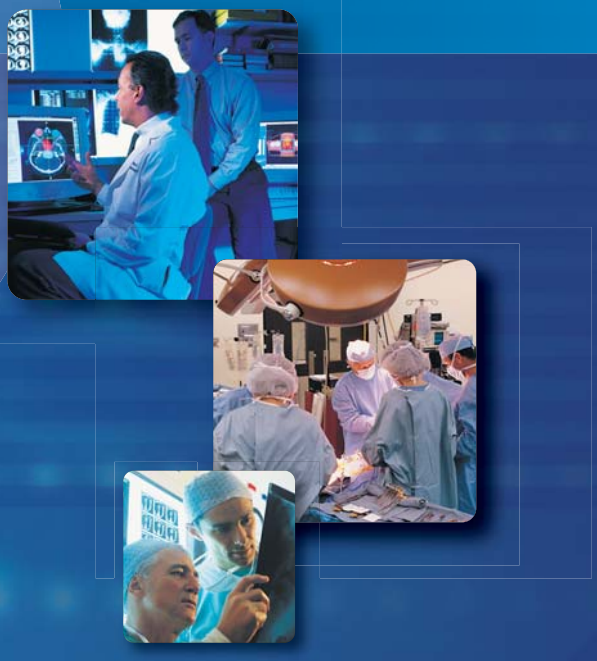
TECHNOLOGY REPORT

HTA

Issue 97

December 2007

Adalimumab, alefacept, efalizumab, etanercept, and infliximab for severe psoriasis vulgaris in adults: budget impact analysis and review of comparative clinical- and cost-effectiveness



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Cite as: Boudreau R, Blackhouse G, Goeree R, Mierzwinski-Urban M. *Adalimumab, alefacept, efalizumab, etanercept, and infliximab for severe psoriasis vulgaris in adults: budget impact analysis and review of comparative clinical- and cost-effectiveness* [Technology report number 97]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2007.

Production of this report is made possible by financial contributions from Health Canada and the governments of Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Northwest Territories, Nova Scotia, Nunavut, Ontario, Prince Edward Island, Saskatchewan, and Yukon. The Canadian Agency for Drugs and Technologies in Health takes sole responsibility for the final form and content of this report. The views expressed herein do not necessarily represent the views of Health Canada, or any provincial or territorial government.

CADTH is funded by Canadian federal, provincial, and territorial governments.

Legal Deposit – 2007
National Library of Canada
ISBN: 978-1-897465-34-9 (print)
ISBN: 978-1-897465-35-6 (online)
I3011 – December 2007

PUBLICATIONS MAIL AGREEMENT NO. 40026386
RETURN UNDELIVERABLE CANADIAN ADDRESSES TO
CANADIAN AGENCY FOR DRUGS AND TECHNOLOGIES IN HEALTH
600-865 CARLING AVENUE
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Canadian Agency for Drugs and Technologies in Health

Adalimumab, Alefacept, Efalizumab, Etanercept, and Infliximab for Severe Psoriasis Vulgaris in Adults: Budget Impact Analysis and Review of Comparative Clinical- and Cost-Effectiveness

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December 2007

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Health technology assessment (HTA) agencies face the challenge of providing quality assessments of medical technologies in a timely manner to support decision making. Ideally, all important deliberations would be supported by comprehensive health technology assessment reports, but the urgency of some decisions often requires a more immediate response.

The Health Technology Inquiry Service (HTIS) provides Canadian health care decision makers with health technology assessment information, based on the best available evidence, in a quick and efficient manner. Inquiries related to the assessment of health care technologies (drugs, devices, diagnostic tests, and surgical procedures) are accepted by the service. Information provided by the HTIS is tailored to meet the needs of decision makers, taking into account the urgency, importance, and potential impact of the request.

Consultations with the requestor of this HTIS assessment indicated that a review of the literature would be beneficial. The research question and selection criteria were developed in consultation with the requestor. The literature search was carried out by an information specialist using a standardized search strategy. The review of evidence was conducted by one internal HTIS reviewer. The draft report was internally reviewed and externally peer-reviewed by two or more peer reviewers. All comments were reviewed internally to ensure they were addressed appropriately.

Reviewers

CADTH takes sole responsibility for the final form and content of this bulletin. The statements and conclusions in this bulletin are those of CADTH and not of the reviewers.

Reviewers who agreed to be acknowledged include:

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Dr. Chih-Ho Hong has received honoraria from Astellas and Schering and has performed clinical trials for Astellas, Serono, Biogen-Idec, and Amgen-Wyeth. Dr. Hong was also an advisor for Schering, Biogen-Idec, and Astellas.

The Health Technology Inquiry Service (HTIS) is an information service for those involved in planning and providing health care in Canada. HTIS responses are based on a limited literature search and are not comprehensive, systematic reviews. The intent is to provide a list of sources and a summary of the best evidence on the topic that CADTH could identify using all reasonable efforts within the time allowed. HTIS responses should be considered along with other types of information and health care considerations. The information included in this response is not intended to replace professional medical advice, nor should it be construed as a recommendation for or against the use of a particular health technology. Readers are also cautioned that a lack of good quality evidence does not necessarily mean a lack of effectiveness, particularly in the case of new and emerging health technologies, for which little information can be found but which may in future prove to be effective. While CADTH has taken care in the preparation of the report to ensure that its contents are accurate, complete, and up-to-date, CADTH does not make any guarantee to that effect. CADTH is not liable for any loss or damages resulting from use of the information in the report.

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ABBREVIATIONS

BIA	budget impact analysis
BIW	twice a week
BMJ	*British Medical Journal*
BSA	body surface area
CADTH	Canadian Agency for Drugs and Technologies in Health
CBC	complete blood count
CD4	cluster of differentiation 4
CDP	complete blood count with differential
CNS	central nervous system
DERP	Drug Effectiveness Review Project
DLQI	Dermatology Life Quality Index
FDA	Food and Drug Administration
HRQoL	health-related quality of life
HIV	human immunodeficiency virus
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
IM	intramuscular
IQR	inter-quartile range
ITT	intention to treat
IV	intravenous
MCO	managed care organization
MID	minimally important difference
NA	not applicable
NHS R&D	National Health Service Research and Development
NR	not reported
PASI	Psoriasis Area and Severity Index
PGA	Physician Global Assessment
PUVA	ultraviolet A plus psoralen
QALY	quality-adjusted life-year
QoL	quality of life
QW	once a week
RCTs	randomized controlled trials
SA	sensitivity analysis
SC	subcutaneous
SR	systematic review
TB	tuberculosis
TIM	targeted immune modulator
TNF	tumour necrosis factor

Title: Adalimumab, alefacept, efalizumab, etanercept, and infliximab for severe psoriasis vulgaris in adults: budget impact analysis and review of comparative clinical- and cost-effectiveness

Date: September 7, 2007

EXECUTIVE SUMMARY

Context and policy issues

Psoriasis vulgaris, also known as plaque psoriasis, is a chronic inflammatory disease characterized by raised, inflamed, red lesions that are covered by silvery white scales. It is typically found on the elbows, knees, scalp, and lower back. The prevalence of psoriasis in Canada has been estimated to be between 1.0% to 2.0%. Approximately 85.0% of patients with psoriasis suffer from plaque psoriasis, 25.0% of whom have a severe form of the disease. Patients with plaque psoriasis experience physical discomfort and emotional distress. There is no cure for plaque psoriasis. Treatment is focused on management of the condition, with the aim of reducing the number, size, and severity of the lesions.

There are several management options for adults who suffer from plaque psoriasis. These include topical treatment, light therapy, and systemic therapy. Patients may also be prescribed a combination of these therapies. Systemic therapy, however, is usually reserved for cases of severe plaque psoriasis. In Canada, efalizumab, alefacept, etanercept, and infliximab are the targeted immune modulators (TIMs) indicated for the treatment of moderate to severe chronic plaque psoriasis in patients who are candidates for systemic therapy, especially those patients with plaque psoriasis that is refractory to other treatments. Adalimumab, another TIM, is not currently indicated for plaque psoriasis, only psoriatic arthritis. TIMs block the action of immune cells that are responsible for plaque psoriasis. They are more specific than other systematic therapies and phototherapies that broadly affect the immune system.

Severe psoriasis is a relatively new indication for the TIMs, and Canadian drug plans are receiving submissions from industry for drug coverage. To facilitate evidence-informed decisions, this report provides comparative evidence on the clinical and cost-effectiveness of adalimumab, alefacept, efalizumab, etanercept, and infliximab and provides a budget impact analysis based on these treatments being reimbursed by public drug plans.

Research questions

1. What is the comparative clinical benefit and long-term harm of adalimumab, alefacept, efalizumab, etanercept, and infliximab for the treatment of adult patients with severe plaque psoriasis?
2. What is the optimal dose of adalimumab, alefacept, efalizumab, etanercept, and infliximab for the treatment of adult patients with severe plaque psoriasis?
3. What is the comparative cost-effectiveness of adalimumab, alefacept, efalizumab, etanercept, and infliximab for the treatment of adult patients with severe plaque psoriasis?
4. What is the budget impact for funding treatment with adalimumab, alefacept, efalizumab, etanercept, or infliximab for one year for all Canadian adults with severe plaque psoriasis?

Methods

Published literature was obtained by cross-searching several electronic databases. Retrieval was limited by human population and publications from 2002 to August 7, 2007. Filters were applied to limit the retrieval to systematic reviews (SRs), clinical studies, and economic studies. The web sites of regulatory agencies and health technology assessment (HTA) and related agencies were searched, as were specialized databases such as those of the University of York Centre for Reviews and Dissemination. The Google search engine was used to search for information on the Internet. The manufacturers of all commercially available TIMs were asked to provide relevant information.

The clinical review included HTAs, SRs, meta-analyses, randomized controlled trials (RCTs) and observational studies (lasting more than one year and reporting on adverse events or QoL) that focused on comparative (head-to-head) evidence, and HTAs, SR, or meta-analyses comparing more than one TIM on at least one efficacy, clinical effectiveness, or QoL outcome. Reports were included if the TIM was administered as a monotherapy and where the patients had severe plaque psoriasis with baseline BSA ≥10% and PASI ≥10.

For the economic review, reports were included if they described the severity of severe plaque psoriasis, the use of TIMS, and the cost or economic analysis between at least two TIMs. Articles that compared one TIM with standard care or with non-TIM drugs were excluded, as were studies that provided only cost or cost-effectiveness results from other published studies. A four-step approach was used to estimate the budget impact of TIMs in Canada.

Findings

Clinical effectiveness of TIMs for severe plaque psoriasis

No comparative trials were found. One HTA and one SR were retrieved that assessed more than one TIM on at least one clinical outcome. Six RCTs that focused on the dosing of TIMs were included.

Three common clinical outcomes reported in the literature were included in this CADTH report: achieving a Psoriasis Area and Severity Index (PASI) score of 75% (i.e., PASI 75), achieving a responder status (usually a score of 0, 1, or 2) on the Physician Global Assessment (PGA), and the percent or score difference in the Dermatology Life Quality Index (DLQI) (a percent or point decrease indicates improvement).

The authors of the HTA concluded that etanercept and efalizumab are efficacious for patients with moderate to severe plaque psoriasis when PASI 75 is measured at 12 or 24 weeks after therapy initiation. The SR found that patients taking alefacept, etanercept, or efalizumab reported improvements in PASI, DLQI, and PGA scores (when these scores were reported). No statistical analyses were reported for adverse events.

Of the six RCTs that focused on dosing, two (one assessing efalizumab and one assessing etanercept) did not report any *P* values for the different dosing regimens. Of the remaining four, two assessed etanercept, and two assessed infliximab. One infliximab trial reported that significantly more patients achieved PASI 75 when given 5 mg infliximab over 3 mg infliximab, and the second infliximab trial reported that significantly more patients achieved PASI 75 when on a continuous maintenance therapy than when on intermittent maintenance therapy. One etanercept trial reported that there was no significant difference between a maintenance schedule of 25 mg twice a week compared to 50 mg twice a week. The second etanercept trial reported that patients were significantly more likely to be PGA responders (score of 0, 1, or 2) if they were on continuous maintenance therapy rather than interrupted maintenance therapy.

Cost-effectiveness of TIMs for severe plaque psoriasis

Five costing studies were included in the economic review. None were Canadian studies. The studies that investigated the one year US treatment cost of psoriasis treatment, however, provided fairly consistent estimates of the costs of TIMs. Estimates of annual costs with alefacept ranged from $16,000 to $17,910. Efalizumab cost estimates ranged from $18,290 to $19,728. Etanercept cost estimates ranged from $17,700 to $34,800. The variation in these estimates is due to different assumptions on dosing regimens. One costing study estimated the one year cost of infliximab ($17,700 5 mg/kg dosing; $34,300 10 mg/dosing) and adalimumab ($17,700, 40 mg every other week; $34,800 40 mg every week).

Seven economic evaluations were included. None of the cost-effectiveness analyses were conducted from a Canadian perspective. Several methodological issues were identified and these were common to the studies. First, few of the

studies conducted a proper multi-comparator cost-effectiveness analysis. Proper conclusions on cost-effectiveness cannot be made using average ratios as was done in the cost-effectiveness studies being reviewed. Second, only one cost-effectiveness study used utility measures or quality adjusted life years (QALYs) as outcomes, thus limiting the comparability of cost-effectiveness results to common $/QALY benchmarks or to cost-effectiveness found in other disease areas. Lastly, all cost-effectiveness studies were limited to one year despite the fact that severe psoriasis is a chronic disease with negative impacts on quality of life.

Budget impact analysis of TIMs for severe plaque psoriasis

The Canadian annual cost of treating adults with severe plaque psoriasis with a TIM on public drug plans was estimated to be $30.1 million. This estimate was sensitive to assumptions on Canadian psoriasis prevalence rates and on assumptions of the proportion of patients that would transfer treatment from oral systemics to treatment with a TIM.

Conclusions and implications for policy making

Because of the non-existence of comparative trials or meta-analyses using indirect comparisons, no comparative conclusions can be made regarding the relative efficacy of TIMs for the treatment of adults with severe plaque psoriasis. Relative to placebo, each TIM therapy (except adalimumab, for which no information was retrieved) resulted in the clinical improvement of plaque psoriasis as measured by scores on the PASI, PGA, and DLQI in the short term (up to 24 weeks).

No conclusions regarding adverse events associated with TIMs for periods longer than one year could be made because the information retrieved was limited to one HTA and one SR, neither of which reported statistical information on adverse events. Advisory warnings regarding treatment with adalimumab, alefacept, efalizumab, etanercept, and infliximab have come from Canadian and international organizations. Since 2000, there have been 24 advisories about the use of TIMs in adults. The most common warnings were regarding opportunistic infection (especially tuberculosis), malignancies, and hepatitis B reactivation. All three were noted for adalimumab, etanercept, and infliximab.

Limited evidence was found on the dosing of infliximab and etanercept therapy. No advantage to any dosing regimen for these two therapies emerged in the literature. Some evidence was found suggesting that a continuous maintenance therapy, as opposed to an "as needed" maintenance therapy, may be more effective with infliximab. For patients taking etanercept, there was evidence that providing continuous maintenance therapy resulted in more patients achieving or maintaining a "clear" or "almost clear" score (0, 1, or 2) on the PGA. No RCT reported *P* values for the different dosing regimens. Thus, no conclusions about the observed differences in rates of adverse events could be made, and it is unclear whether there is a dose-dependent association with any adverse event(s).

The TIMs differ in terms of mode of action and mode of administration, complicating meaningful comparisons of clinical effectiveness. In addition, longer term (>24 weeks) data from well-designed, controlled, comparative studies are needed to assess the efficacy, effectiveness, and harm in patients with severe plaque psoriasis. No literature was retrieved on adalimumab therapy for the off-label indication of plaque psoriasis.

The Canadian annual cost of treating adult patients with severe plaque psoriasis with a TIM was estimated to be $30.1 million. This estimate was sensitive to assumptions on Canadian psoriasis prevalence rates and on assumptions about the proportion of patients taking an oral systemic who would transfer to treatment with a TIM. The budget impact analysis was based on standard recommended dosing regimens and did not take possible "dose creep" into account for any TIM. Given the potential budget impact of funding TIMs for severe plaque psoriasis, comparative information on the long-term benefits, harms, and cost-effectiveness of these

agents should be gathered to support funding decisions.

1 CONTEXT AND POLICY ISSUES

Psoriasis vulgaris, also known as plaque psoriasis, is a chronic inflammatory disease characterized by raised, inflamed, red lesions that are covered by silvery white scales. It is typically found on the elbows, knees, scalp, and lower back.[1] The prevalence of psoriasis in Canada has been estimated to be between 1.0% to 2.0%.[2,3] Approximately 85.0% of patients with psoriasis suffer from plaque psoriasis;[4] and 25.0% of patients with plaque psoriasis have a severe form of the disease.[5]

For this report, a patient with severe plaque psoriasis is defined as having psoriasis on ≥10.0% of his or her body surface area (BSA)[6,7] and a score of at least 10 on the Psoriasis Area and Severity Index (PASI).[7] PASI is a test that is administered by dermatologists to measure the intensity of the disease. PASI is used to measure the basic physical characteristics of psoriasis. The score reflects the severity of psoriasis, whereas BSA is used to measure the area affected on the patient's body. The quality of life (QoL) is not considered when classifying the severity of the patient's disease.[8,9]

Because there is no best measure used to assess plaque psoriasis in clinical trials, three of the most common clinical outcomes reported in the literature were selected a priori, in consultation with a clinical expert, for this CADTH report: the PASI, the Physician Global Assessment (PGA), and the Dermatology Life Quality Index (DLQI).

The most commonly used standardized measure of disease severity is the PASI, which is used to score the severity of the psoriasis based on the redness, scaliness, and thickness of the lesions and the body surface area that is affected.[10] Scores range between zero for no disease and 72 for maximal disease.[11] PASI is measured at baseline and during or after treatment. PASI 50 and PASI 75 are commonly used scores used to evaluate the percentage of improvement of the PASI from baseline. A PASI 50 refers to a 50% improvement in the score, while a PASI 75 refers to a 75% improvement in the score. This CADTH report will focus on PASI 75 because it is the most common (i.e., well-established) primary clinical endpoint in the literature.[11] While PASI 75 is often considered to be a clinically meaningful improvement, there is no universally accepted definition of a clinically meaningful difference. Patients may have a PASI score of less (i.e., ≤PASI 75) yet deem their disease to be meaningfully improved.[10,11]

A second commonly reported measure in the literature is the PGA, which measures the physician's impression of the disease. The minimum score is zero, which indicates that the patient is clear of psoriasis, and the maximum score is 5, which indicates severe psoriasis.[10] The standard form of this measure is the static form, which measures the physician's impression at a point in time. The second form of the measure is the dynamic form, which a physician uses to assess the global improvement in the disease compared to baseline.[10]

A third tool to assess disease severity, the DLQI, is a health-related quality of life (HRQoL) measure. The DLQI is a 10-item questionnaire with six domains that relate to different aspects of a person's life such as daily activities, personal relationships, and leisure.[8,11] The total score ranges between zero for no impairment of HRQoL to 30 for maximum impairment, with a negative change score indicating HRQoL improvement over time.[8,11] There is debate regarding what change in score reflects a clinically meaningful result, although a change of five points in either direction is considered to be clinically meaningful.[8]

Plaque psoriasis is an autoimmune disorder involving the erroneous activation of T-cells, which trigger other immune responses (e.g., activation of cytokines) that lead to inflammation and rapid turnover of skin cells.[12] Patients with plaque psoriasis experience physical discomfort and emotional distress.[11,13] There is no cure for plaque psoriasis. Treatment is focused on management of the condition to

reduce the number, size, and severity of the lesions.[12]

There are several management options for adults who suffer from plaque psoriasis. These include topical treatment (e.g., corticosteroid, retinoid, coal tar, salicylic acid), light therapy [e.g., natural sunlight, ultraviolet B phototherapy, and ultraviolet A plus psoralen (PUVA) phototherapy], and systemic therapy [e.g., methotrexate, cyclosporine, and targeted immune modulators (TIMs)].[6] Patients may also be prescribed a combination of these therapies. Systemic therapy, however, is usually reserved for cases of severe plaque psoriasis.[14]

In Canada, efalizumab,[15] alefacept,[16] etanercept,[17] and infliximab[18] are the TIMs that are used in the treatment of severe chronic plaque psoriasis among adult patients who are candidates for systemic therapy, especially those with plaque psoriasis that is refractory to other treatments.[14] Efalizumab[15] and etanercept[17] are delivered via subcutaneous (SC) injection, alefacept[16] is delivered via intramuscular (IM) injection, and infliximab[18] is delivered via intravenous (IV) injection. Adalimumab is not indicated for plaque psoriasis, only psoriatic arthritis. Its route of administration is via SC injection.[19]

TIMs block the action of immune cells that are responsible for plaque psoriasis. They are more targeted than other systematic therapies and phototherapies, which have a broad impact on the immune system.[20] Infliximab, adalimumab, and etanercept are tumour necrosis factor (TNF)-α inhibitors while efalizumab inhibits T-cell activation and proliferation.[19,21] Alefacept reduces the number of memory-effector T-cells and blocks the activation of T-cells.[21] More information on dosing and mechanism of action for each biologic appears in Appendix 1 Table 1.

Severe psoriasis is a new indication for the TIMs, and Canadian drug plans are receiving submissions from industry for drug coverage. To facilitate evidence-informed decisions, this report provides comparative evidence on the clinical- and cost-effectiveness of adalimumab, alefacept, efalizumab, etanercept, and infliximab and provides a budget impact analysis based on these treatments being reimbursed by public drug plans.

2 RESEARCH QUESTIONS

1. What is the comparative clinical benefit and long-term harm of adalimumab, alefacept, efalizumab, etanercept, and infliximab for the treatment of adult patients with severe plaque psoriasis?

2. What is the optimal dose of adalimumab, alefacept, efalizumab, etanercept, and infliximab for the treatment of adult patients with severe plaque psoriasis?

3. What is the comparative cost-effectiveness of adalimumab, alefacept, efalizumab, etanercept, and infliximab for the treatment of adult patients with severe plaque psoriasis?

4. What is the budget impact for funding treatment with adalimumab, alefacept, efalizumab, etanercept, and infliximab for one year for all Canadian adults with severe plaque psoriasis?

3 METHODS

3.1 Literature Search

Published literature was obtained by cross-searching Biosis, Embase, and Medline databases on the OVID search system. Parallel searches were performed on PubMed and the Cochrane Library (Issue 2, 2007) databases. Regular alerts were established on Biosis, Embase, Medline, and PubMed. The information retrieved via alerts is current to August 7, 2007. Retrieval was limited by human population and publications from 2002 to August 7, 2007. Filters were applied to limit the retrieval to systematic reviews (SRs), clinical studies, and economic studies.

The web sites of regulatory agencies and health technology assessment (HTA) and related

agencies were searched, as were specialized databases such as those of the University of York Centre for Reviews and Dissemination. The Google search engine was used to search for information on the Internet.

The manufacturers of all commercially available TIMs were asked to provide relevant information.

3.2 Eligibility Criteria for Clinical Review

A priori inclusion criteria consisted of HTAs, SRs, or meta-analyses, comparative (i.e, non-placebo controlled) randomized controlled trials (RCTs), and controlled observational studies that extended past one year of observation and reported on QoL measures or adverse events. Studies were excluded if they lacked an active TIM comparator group. After the literature search was completed, however, no comparative RCTs had been identified. Thus, no HTAs, SRs, or meta-analyses that fulfilled the inclusion criteria could be retrieved. Consequently, the inclusion criteria were expanded to include HTAs, SRs, or meta-analyses that compared more than one TIM on at least one efficacy, clinical effectiveness, or QoL outcome. Because longer term harm data were the focus of this report, harm data were collected from those observational studies (with control) groups and any placebo-controlled RCTs that exceeded one year in duration (before any trial cross-over), and from dosing RCTs (regardless of trial duration) to enable a more complete comparison of dosing regimens between TIMs. This CADTH report included only those reports where the TIM was administered as a monotherapy and where the focus was on adult patients with severe plaque psoriasis (i.e., patients with baseline BSA≥10% and baseline PASI≥10).

3.3 Eligibility Criteria for Economic Review

The inclusion criteria specified reports that described the severity of severe plaque psoriasis, the use of TIMS, and the cost or economic analysis between at least two TIMs. Articles that compared one TIM with standard care or with non-TIM drugs were excluded, as were studies that provided only cost or cost-effectiveness results from other published studies.

3.4 Method of Budget Impact Analysis

A four-step approach was used to estimate the budget impact of TIMs in Canada. In the first step, the proportion of the Canadian population who would use a TIM for the treatment of severe plaque psoriasis was estimated. Second, the average annual TIM treatment cost was calculated. Third, the number of Canadians on public health plans was estimated. Finally, the budget impact was calculated by multiplying the estimates derived in the first three steps.

3.4.1 Estimating proportion of population who would use TIMs for severe plaque psoriasis

A top-down approach using published data sources was used to estimate the proportion of the Canadian adult population who would be treated for severe plaque psoriasis with a TIM. The prevalence of psoriasis in Canada has been estimated to be between 1.0% to 2.0%.[2,3] Therefore, the prevalence of psoriasis used in the calculations was assumed to be 1.5% for the base-case analysis. Prevalence rates of 1.0% and 2.0%, however, are assumed in the sensitivity analysis. Furthermore it was assumed that among all psoriasis patients, 85.0% have plaque psoriasis[4] and that of all plaque psoriasis patients, 25.0% have a severe form of the disease.[5]

It was assumed that 18% of severe plaque psoriasis patients are on systemic oral therapy.[22] According to the literature, 16.0% to 30.0% of patients are intolerant or unresponsive to non-TIM systemic therapies.[23,24] Based on this information, for the base-case analysis, it was assumed that 23.0% (midpoint of 16.0% and 30.0%) of patients on systemic therapy would

move to treatment with a TIM. This percentage was varied from 10.0% to 85.0% in the sensitivity analyses.

The proportion of the Canadian population suffering from severe plaque psoriasis who would receive TIM therapy was estimated to be 0.000132 (0.0132%). A summary of the assumptions used to calculate this number appears in Appendix 5 Table 1.

3.4.2 Estimating annual cost of treatment with a TIM

The estimation of the annual cost of treatment of severe plaque psoriasis treatment with a TIM was done in several stages. First, the average medication unit cost for each TIM in Canada was collected. Second, the dosing regimens required for one year of treatment with each TIM was determined. Based on the unit drug costs and the dosing regimen, an annual cost of treatment for each of the five TIMs was calculated on a per patient basis. Finally, an average annual treatment cost with a TIM was calculated by weighting the costs of the five TIMs by the estimates of market share for each.

The unit cost of each TIM was based on the average reimbursement price from all provincial formularies that listed prices for the drug. The costs of alefacept and efalizumab were unavailable from any of the provincial formularies. Therefore, PPS Pharma[25] was used as the source of the unit prices for these two medications. Appendix 5 Table 2 presents the mean unit cost for each included TIM in the analysis. The annual treatment regimen required for each TIM was based on the Compendium of Pharmaceutical Services[26] and on advice from a clinical expert (Jerry Tan, MD, FRCP, Dermatologist, Windsor, ON: personal communication, 2007 summer). Annual treatment regimens were assumed to differ based on whether it was the first year of treatment or a subsequent year of treatment. Appendix 5 Table 3 presents the annual treatment regimens assumed in the model by first or subsequent years of treatment.

Based on their average unit costs and annual dosing regimens, the annual treatment costs of each TIM were calculated. The dosage of efalizumab and infliximab is based on the patient's weight, which was assumed to be 90 kg on average per patient. In the sensitivity analysis, the average weight is assumed to be between 80 kg and 100 kg. Because efalizumab and infliximab are dispensed in vials, it was assumed that if any part of a vial was used in a treatment, the cost of the entire vial would be incurred. Separate costs for the first year of treatment and subsequent years of treatment were calculated. In addition, it was assumed that in any given year, 4.0% of patients would be on induction treatment (first year) and 96.0% would be on maintenance therapy (subsequent year).[27] In the sensitivity analysis, this percentage is varied between 0.0% and 100.0%.

The Canadian market share of each TIM was based on data reported in a budget impact analysis (BIA) submitted to CADTH.[28] In this document, the market share of etanercept, infliximab, and efalizumab was estimated to be 0.72, 0.20, and 0.08 respectively, based on Brogan private payer data as of March 2007. The market shares of adalimumab and alefacept were excluded in the BIA. For our analysis, we assumed that adalimumab and alefacept will each have a market share of 0.025. Therefore, the market shares of the other three drugs were adjusted to reach a total market share of 100%. Appendix 5 Table 4, presents the annual first year, subsequent year, and weighted treatment costs for each TIM. Based on the assumption that 4.0% of patients would be on induction treatment, the weighted treatment cost of adalimumab, etanercept, infliximab, alefacept, and efalizumab was estimated to be $18,102, $19,839, $30,647, $29,976, and $21,420 respectively. Based on our market share assumptions, the average annual treatment cost for a TIM was estimated to be $22,223.

3.4.3 Applying Canadian population, proportion treated, proportion on public drug plans, and annual costs of TIM

To estimate the number of adult patients in Canada treated with a TIM in a given year, our estimate of the proportion of the population who would be treated with a TIM was multiplied by the estimated number of adults (18 years and over) in Canada. The number of Canadians who would be treated with a TIM was then multiplied by the proportion of patients who would be on public drug plans. It was assumed that 40.0% of all Canadian psoriasis patients would be covered by public drug plans.[29]

The public drug plan annual costs of treatment with all TIMs was based on the estimated number of public drug plan patients on TIM treatment multiplied by the estimated annual cost of a TIM. Canadian population estimates were taken from Canadian census data.[30]

4 FINDINGS

4.1 Clinical Review

The summary of clinical findings answers two research questions: one pertaining to the clinical effectiveness and the second pertaining to the dosing of TIMs. For the first question, one HTA[11] and one SR[6,31] are summarized. A summary of the evidence pertaining to the second question on dosing is then presented with summaries of the six included RCTs.[7,32-36] A list of reports that describe ongoing trials or were published in languages other than English appears in Appendix 2.

1. **What is comparative clinical benefit and long-term harm of adalimumab, alefacept, efalizumab, etanercept, and infliximab for treatment of adult patients with severe plaque psoriasis?**

4.1.1 Health technology assessment

The objective of the National Health Service Research and Development (NHS R&D) Health Technology Assessment Programme report[11] (from the UK) was to evaluate the clinical effectiveness, harm, tolerability, and cost-effectiveness of etanercept and efalizumab for patients with moderate to severe plaque psoriasis (i.e., BSA≥10%, and PASI=10 to 20). The primary outcome used in the NHS review was the PASI 75. This review included 42 studies (39 were published), of which eight RCTs reported the efficacy of etanercept and efalizumab, 10 studies reported adverse events, and 24 RCTs reported the efficacy of other treatments (22 RCTs were on non-TIMs and two were on infliximab) for plaque psoriasis. Literature was searched until April 2004. Of the eight RCTs assessing efficacy, three were on etanercept (n=1,347) and five were on efalizumab (n=2,963). All RCTs were placebo-controlled.

The results of the three etanercept RCTs were pooled; 33.0% of patients taking etanercept 25 mg twice a week achieved a PASI 75 at 12 weeks. The pooled relative risk (RR) of achieving PASI 75 was 10.69 (95% CI: 6.15 to 18.57) in favour of etanercept over placebo. Two of the three RCTs reported the percentage of DLQI reduction, with one reporting a 50.8% reduction and the other reporting a 61.0% reduction (which means improvement in HRQoL) after 12 weeks of therapy (25 mg twice a week). At 50 mg twice a week, the pooled results from two RCTs showed that 49.0% of patients achieved PASI 75 after 12 weeks, with a pooled RR of achieving PASI 75 of 14.80 (95% CI: 8.40 to 26.06) favouring etanercept over placebo. No DLQI scores were reported for those treated with 50 mg twice a week. It is unclear how the pooled RRs were calculated, because few or no details were provided on the statistical methods used for meta-analysis. The most common adverse event reported by patients taking etanercept was injection site reaction. Other common adverse events found in RCTs and in the uncontrolled trials were headache, infection, and upper respiratory tract infection (no *P* values reported). These adverse events

were specific to 12- and 24-week treatment. Longer term treatment harm analyses for plaque psoriasis were lacking.

The five RCTs on efalizumab yielded a PASI 75 for 27.0% of the patients after 12 weeks of therapy. One RCT reported that 26.6% of patients received clear or minimal psoriasis status after 12 weeks of treatment. Three of the five RCTs included patients (n=1,130) who were treated with 1 mg/kg once a week. When pooled, they yielded a RR of achieving PASI 75 of 6.34 (95% CI: 4.27 to 9.42) favouring efalizumab over placebo. The mean percentage decrease on the DLQI, from three RCTs, was approximately 46.0%. As with the NHS's meta-analyses of etanercept, it is unclear as to how the pooled RRs were calculated. The authors of the NHS HTA stated that longer term data could not be extracted because of poor reporting and inconsistent dosing across trials. There was a lack of information on serious infection and serious adverse events. The withdrawal rates due to adverse events were low (authors do not quantify "low"). Commonly reported adverse events at 12 weeks were headache, chills, nausea, myalgia, pain, and fever. The authors reported that the (small) amount of longer term adverse event data (up to three years) appeared to be similar to what was reported at 12 weeks.

From the 24 RCTs that assessed other treatments (i.e., non-TIM) for psoriasis, two were placebo-controlled RCTs on infliximab. One trial included patients with BSA >5.0%, which would not fulfill the inclusion criteria for this CADTH report. The second RCT included infliximab doses of 3 mg/kg and 5 mg/kg, which resulted in a RR of achieving PASI 75 of 12.19 (95% CI: 4.04 to 36.80) for 3 mg/kg and a RR of 13.94 (95% CI: 4.97 to 44.89) for 5 mg/kg, both of which favour infliximab over placebo. Reported adverse events included fever, chills, pruritus, chest pains, hypotension, viral infections, lupus-like syndrome, anaphylactic reactions, upper and lower respiratory tract infections, dry skin, fatigue, and myalgia. No further details (e.g., incidence) were provided.

The authors of the NHS HTA concluded that etanercept and efalizumab are efficacious for the treatment of moderate to severe plaque psoriasis. They cautioned, however, that the trial populations may not have reflected the difficult to treat population for whom etanercept and efalizumab are licensed. Therefore, the authors indicated a need for conducting trials that enrol such patients and for longer term trials to better assess the efficacy and harm of etanercept and efalizumab. No conclusions regarding infliximab were reported.

4.1.2 Systematic review

The Drug Effectiveness Review Project (DERP) published a report on TIMs in 2007.[6,31] Several indications were examined, including patients with plaque psoriasis, BSA≥10%, and minimum PASI ranging between 10 and 12 (DERP authors labelled these patients as having severe plaque psoriasis). The three research questions assessed comparative clinical effectiveness (e.g., pain, remission, QoL), comparative incidence and severity of complications, and whether clinical effectiveness or adverse events differed by subgroup (e.g., age, ethnic group).

From the literature search that spanned 1980 to August 2006, the following 13 double-blinded placebo-controlled RCTs were included: two on alefacept (n=736), four on etanercept (n=1,985), four on efalizumab (n=2,177), three on infliximab (n=1,462), and none on adalimumab. The reported trial length (excluding any open-label extension of the studies) was 12 or 24 weeks for all studies except one, which reported a study duration of 50 weeks (although the health outcomes were reported only for week 10). The sample sizes of individual RCTs ranged between 112 and 835. All trials assessed PASI 50 or PASI 75, and most included a QoL measure such as DLQI.

Two trials on alefacept were included; both had a follow up of 24 weeks. One trial did not report PASI 75. It reported a significant improvement from baseline of DLQI scores between the 15 mg alefacept group and placebo (4.9 for the alefacept group and 2.7 for placebo, $p<0.001$). While the 10 mg alefacept patients also experienced DLQI improvement, it was not statistically significant (no *P* value reported).

The second RCT on alefacept found that PASI 75 was achieved by 33.0% of patients at 0.150 mg/kg, 31.0% of patients at 0.075 mg/kg, and 19.0% of patients at 0.025 mg/kg.

Four RCTs assessed etanercept, with doses ranging between 25 mg once a week and 50 mg twice a week, and follow-up periods ranging between 12 and 24 weeks. One trial used a dose of 25 mg once a week and reported that at 12 weeks, 14.0% of patients achieved PASI 75. A dose of 25 mg twice a week (three trials) at 12 weeks resulted in 30.0% (one trial) and 34.0% (two trials) of patients achieving PASI 75 compared with 56.0% of patients achieving PASI 75 at 24 weeks with the same dose. Three trials reported that the percentage of PASI 75 achievers was between 47.0% and 49.0% after 12 weeks of etanercept at 50 mg twice a week. Two trials reported a mean percentage improvement of DLQI between 64.0% and 70.0% at 12 weeks (dosing was 25 mg twice a week or 50 mg twice a week). One trial reported 50.0%, 63.0%, and 54.0% improvement in DLQI scores at 12 weeks for doses of 25 mg once a week, 25 mg twice a week, and 50 mg twice a week respectively.

Four trials assessed efalizumab at doses of 1 mg or 2 mg per week. The follow up was 12 weeks. Two trials reported PASI 75 and found that 26.0% to 38.0% of patients achieved this clinical outcome. One trial reported that patients experienced a 40.2% decrease in DLQI. Another trial reported that approximately one third of patients were given a minimum of clear on the static PGA.

Three trials assessed infliximab, with doses of 3 mg/kg/dose IV or 5 mg/kg/dose IV. The follow up was reported to be between 10 and 50 weeks. All endpoints reported here, however, were measured at week 10. Two trials reported PASI 75, which was achieved by 70.3% and 88.0% of patients. It is unclear what the percentage of PASI 75 achievers were in the third trial (80.0% or 57.0%). Two trials reported that patients taking infliximab experienced DLQI score reductions of between 8.0 and 10.0 points.

Commonly reported adverse events for alefacept included unrelated accidental injury, dizziness, nausea, infection, headache, and pruritus. For efalizumab, the most common adverse events were headache, infection, and chills. With etanercept, patients most commonly reported upper respiratory infections, headaches, and bruises at the injection sites. Among the most commonly reported adverse events for patients taking infliximab were infection, upper respiratory tract infection, rhinitis, and serious adverse events (unspecified).

Two studies included in the DERP report performed subgroup analyses based on age and found that etanercept and alefacept did not lead to differences in efficacy or adverse events in patients >65 years or <65 years. It was unclear which group included those who were 65 years old. Another study found that patients taking alefacept who were obese or diabetic experienced similar clinical effectiveness and adverse events when compared with patients without these diseases.

The authors of the DERP report assessed the quality of the included trials. Some trials received a "fair" rating while many were rated as "good." The authors stated that the fair ratings were likely due to poor reporting, rather than poor study methods. Allocation concealment was rarely reported. Most of the included studies were industry-funded. The DERP report's authors noted that there were an insufficient number of trials and insufficient consistency in trial design to allow for indirect comparisons to be conducted across the TIMs.

The authors of the DERP report concluded that TIMs were effective for the treatment of severe plaque psoriasis but that a risk-benefit ratio could not be reliably assessed without long-term data on harm.

2. What is optimal dose of adalimumab, alefacept, efalizumab, etanercept, and infliximab for treatment of adult patients with severe plaque psoriasis?

In 2007, Menter *et al.* published the results of a double-blind RCT on the use of infliximab to treat adults with moderate to severe plaque psoriasis.[32] To be included in the RCT, patients had to have a PASI≥12 and a BSA≥10% (the authors labelled such patients as having moderate to severe plaque psoriasis). Patients were typically Caucasian males, which could have implications for the generalizability (i.e., external validity) of the trial's findings.

This study randomized 835 patients to receive 3 mg/kg IV (n=313), 5 mg/kg IV (n=314), or placebo (n=208). Infliximab was given at weeks 0, 2, and 6. At week 14, patients were randomized again to receive continuous treatment (every eight weeks) or intermittent treatment (as needed). Patients stayed on their original 3 mg/kg and 5 mg/kg schedule and were blinded to their maintenance therapy assignment. If PASI<75, the patient received the original infliximab dose but if PASI≥75, then a placebo was given. The treatment timeline went to 46 weeks with patients in the intermittent maintenance therapy being seen as often as every four weeks. The patients in the placebo group stayed in the placebo group for weeks 0, 2, and 6, and were then given 5 mg/kg infliximab at weeks 16, 18, and 22, and every eight weeks thereafter. Intention to treat (ITT) data were reported, and if insufficient data were collected by week 10, then the patient was presumed to not have achieved the primary endpoint. The clinical outcome data appear in Table 1.

At least two-thirds of patients in the 3 mg/kg and 5 mg/kg groups achieved PASI 75 at 10 weeks. No statistical analyses were performed to compare the effectiveness of the two doses, so it cannot be reported whether such differences were statistically significant. The maintenance therapy was evaluated at week 50. When the 5 mg/kg patients who were PASI 75 responders at week 10 were compared, the patients on continuous maintenance therapy had a statistically significantly higher average per cent PASI improvement than did patients on intermittent therapy. The same pattern was seen in the 3 mg/kg group. The mean total dose, on average, was similar between those on continuous therapy and those on intermittent therapy. For the 3 mg/kg group, the average total dose up to week 50 was 22.1 mg/kg for the continuous group compared with 20.1 mg/kg for the intermittent group. For the 5 mg/kg group, the average total dose was 37.1 mg/kg for the continuous group and 30.2 mg/kg for the intermittent group. The statistical significance of such differences in total dose was not reported.

When the average per cent improvement in PASI between week 2 and week 50 was compared across dose and intermittent maintenance strategy, it was found that patients in the 5 mg/kg intermittent group had a higher average PASI improvement than the 3 mg/kg intermittent group [73.5%, inter-quartile range (IQR): 63.4% to 89.4% compared with 65.5%; IQR: 51.0% to 84.7%, $P = 0.003$]. The authors concluded that 3 mg/kg and 5 mg/kg were both effective doses. The 5 mg/kg dose administered every eight weeks resulted in greater efficacy at 50 weeks.

Gottlieb *et al.* published the results of a double-blinded RCT (n=249) that compared 3 mg/kg or 5 mg/kg of infliximab in adults with moderate to severe plaque psoriasis.[7] To be included, patients had to have a PASI≥12 and a BSA≥10%. Patients were typically male and had a median age of 44 years. Patients were randomized to receive 3 mg/kg IV or 5 mg/g IV at weeks 0, 2, and 6. The percentage of patients achieving PASI 75 was measured at 10 weeks. The analyses were reported to be ITT, but it is unclear whether patients who did not receive any doses of the study drug were included. The authors carried the last observation forward, and if the available data were insufficient, then the patient was deemed to not have achieved the primary outcome. The clinical outcome data appear in Table 1.

It was reported that patients who were given 5 mg/kg (n=99) of infliximab were statistically more likely to reach a PASI 75 endpoint than patients given 3 mg/kg (n=99). After week 10, the percentage of patients achieving PASI 75 in the 3 mg/kg group started to decline, whereas a decline in patients achieving PASI 75 in the 5 mg/kg group was evident after week 14.

By week 10, DLQI scores were near normal, with scores of 2 for the 3 mg/kg group and 1 for the

5 mg/kg group. Static PGA was also measured, with 71.7% and 89.9% (for 3 mg/kg and 5 mg/kg respectively) of patients achieving a minimal or cleared score from the physician.

Gottlieb *et al.* concluded that patients with moderate to severe psoriasis showed statistically significant clinical improvement (through PASI and DLQI) with 3 mg/kg and 5 mg/kg doses of infliximab, when compared to placebo.

Papp *et al.* published findings comparing two doses of etanercept administered in adults with moderate to severe plaque psoriasis.[35] Patients had BSA≥10% and PASI≥10. Patients were randomized to receive placebo (n=193), etanercept 25 mg SC twice a week (n=196), or etanercept 50 mg SC twice a week (n=194) for 12 weeks. After the first 12 weeks, all patients were assigned to receive 25 mg twice a week for an additional 12 weeks. The primary endpoint was a PASI 75 at 12 weeks of treatment. A secondary endpoint was the static PGA. The same endpoints were measured at 24 weeks. Patients were typically Caucasian and male, with a median age of 45 years (Table 1).

At 12 weeks, PASI 75 was achieved by 49.0% of the etanercept 50 mg twice a week group and 34.0% of patients in the etanercept 25 mg twice a week group. A sensitivity analysis was performed by imputing missing data with a value that indicated a non-PASI 75 response. The results were similar with 46.0% and 32.0% for etanercept 50 mg twice a week and 25 mg twice a week respectively.

At 24 weeks, all patients were given etanercept 25 mg SC twice a week. No statistically significant difference was found between the percentage of patients achieving PASI 75 for patients originally in the 25 mg twice a week or 50 mg twice a week groups. The authors noted that the power to detect a significant difference was low, with a 38.0% chance of detecting an existing difference between the two groups. A sensitivity analysis was conducted where patients with missing data were assumed not to have met the response criteria for the efficacy endpoint. The result yielded similar PASI 75 results (50.0% of patients in the 50 mg twice a week and 42.0% of patients originally in the 25 mg twice a week group). Of the patients in the 50 mg twice a week group who were PASI 75 responders at the initial 12 weeks, 77.0% (70/91 patients) remained PASI 75 responders at 24 weeks.

The authors reported that patients in all three experimental groups experienced similar proportions of adverse events and infections at 12 and 24 weeks. No statistical analyses were performed.

Papp *et al.* concluded that starting patients with a dose of 50 mg twice a week followed by a maintenance schedule of 25 mg twice a week produced a significant improvement in moderate to severe plaque psoriasis and provided dermatologists with another option in treating patients.

Moore *et al.* published the results of an open-label RCT on two etanercept maintenance therapies for patients with plaque psoriasis and who had BSA≥10% (no severity label was given to the patient population).[34] All patients (n=2,546) were given 50 mg SC twice a week for the initial 12 weeks. After the first 12 weeks, patients continued to receive the 50 mg once a week (continuous group) until week 24 or received the interrupted maintenance therapy. Those patients who were randomized to receive the interrupted maintenance therapy and who had PGA responder status (score of 0, 1, or 2) were discontinued from etanercept therapy until a relapse occurred (loss of PGA responder status), after which 50 mg once a week of etanercept was reinitiated at week 16 or 20 through to week 24. If, after the first 12 weeks, the patients randomized to receive the interrupted maintenance therapy were not PGA responders, they continued to receive etanercept 50 mg once a week through to week 24. The average patient was a Caucasian male of 45.4 years (Table 1).

The primary endpoint was whether the patient achieved PGA responder status at week 24. The secondary endpoints included DLQI. All patients who received at least one dose of the study drug were included in the analyses.

Table 1: Clinical outcomes of dosing studies					
Study	**Sample Size, Dose**	**Duration (weeks)**	**PASI 75 (% patients achieved)**	**DLQI Decrease**	**PGA (% patients)**
Infliximab					
Menter *et al.*[32]	n=835 3 mg 5 mg placebo	10	 70.3* 75.5* 1.9, *P* <0.005	 9.0 pt * 9.0 pt * 0 pt, *P* <0.001 (medians)	 69.8* 76.0* 1.0, *P* <0.001 clear or excellent
	maintenance therapy (week 10 responders) 3 mg: continuous 3 mg: intermittent 5 mg: continuous 5 mg: intermittent	50	 65.5 64.9 76.7 76.5	NR	NR
Gottlieb *et al.*[7]	n=249 3 mg 5 mg placebo	10	 71.7* 87.9* 5.9, *P* <0.001	 8.0 pt† 10.0 pt† 0 pt, *P* <0.001 (median)	 71.7* 89.9* 9.8, *P* <0.001 clear or almost clear
Etanercept					
Papp *et al.*[35]	n=583 25 mg twice a week 50 mg twice a week placebo	12	 34.0* 49.0* 3.0, *P* <0.0001	NR	NR
	maintenance therapy (25 mg twice a week) original group membership: 25 mg twice a week 50 mg twice a week	24	 45.0 54.0, *P* = 0.09	NR	NR
Moore *et al.*[34]	n=2,546 50 mg twice a week	12	NR	NR	71.3 72.0, no *P* value
	maintenance therapy continued interrupted	24	NR	NR	 71.0 59.5, *P* <0.0001 clear or almost clear
Leonardi *et al.*[36]	n=652 25 mg once a week 25 mg twice a week 50 mg twice a week placebo	12	 14.0* 34.0* 49.0* 4.0, *P* <0.001	 47.2%* 50.8%* 61.0% * 10.9, *P* <0.001	 23.0* 34.0* 49.0* 5.0, *P* <0.001 clear or almost clear
Efalizumab					
Gottlieb *et al.*[33]	n=56 0.5 to 1.0 mg/kg 1.0 to 2.0 mg/kg	8	 10.0 30.0, no *P* value	NR	 10.0 21.0, no *P* value scored excellent or better

*=significant compared to placebo; †=unclear reporting but likely significant compared to placebo; DLQI=dermatology life quality index; IQR=inter-quartile range; kg=kilogram; mg=milligram; NR=not reported; PASI=psoriasis area and severity index; PGA=physicians global assessment.

At week 24, more patients in the continuous group were given PGA responder status. The authors reported that this difference was not observed (no *P* values reported) after the initial 12 weeks, with more than two-thirds of each maintenance therapy group achieving PGA responder status. It took an average of 39.6 days to relapse after discontinuing treatment and then took an average of 35.0 days to regain responder status after therapy was restarted.

Moore *et al.* reported that similar adverse and serious adverse events were reported for both treatment groups. They concluded that etanercept can be successfully used and can be reinitiated successfully if therapy is discontinued.

In Leonardi *et al.*'s double-blinded RCT, etanercept was administered to adults with moderate to severe plaque psoriasis (BSA ≥10% and PASI ≥10).[36] Patients were randomly assigned to one of four groups: placebo (n=166), 25 mg SC once a week (n=160), 25 mg SC twice a week (n=162), or 50 mg SC twice a week (n=164) for 12 weeks. After the first 12 weeks, patients in the placebo group unknowingly were switched to the 25 mg twice a week group. Patients tended to be male and Caucasian (Table 1).

The primary endpoint was PASI 75 at 12 weeks with the static PGA and DLQI. All patients who received at least one dose (n=652/672) of the study drug were included in the analyses with the last observations carried forward in cases of missing data or withdrawal from the study. As the dose increased, so did the percentage of people who experienced favourable PASI 75, "clear," or "almost clear" PGA status, and improvement in the DLQI. While the authors mentioned the occurrence of a dose-dependent response pattern, no statistical analyses were conducted among the three dosing groups.

The same outcomes were assessed at 24 weeks (with the same number of patients in each dose group) and the results improved. It is unknown whether any of the differences were statistically significant.

Leonardi *et al.* reported that the adverse event rate and infection rate were observed to be similar between treatment groups, but no statistical analyses were reported. They concluded that dose-dependent improvements were observed. No statistical analyses were reported between dose groups.

Gottlieb *et al.* reported the results of an open-label RCT on the use of efalizumab administered to adult patients with moderate to severe plaque psoriasis.[33] Patients had BSA ≥15% and PASI score ≥12. Patients (n=56) were randomized to one of five dosing groups. The focus of the paper is on two groups: one group (n=23) received a dosing escalation of efalizumab from 0.5 mg/kg SC to 1.0 mg/kg SC, and the second group (n=24) received a dosing escalation of efalizumab from 1.0 mg/kg SC to 2.0 mg/kg SC. Weekly doses were given for eight weeks. The details of the escalation are not provided. Patients were predominantly Caucasian males. There did not seem to be any dropouts or withdrawals in this study, and the analyses seemed to include all randomized patients. Details of the analyses were not reported (Table 1).

PASI scores and PGA were primary endpoints. PASI 75 was achieved by 10.0% of the group who received 0.5 mg/kg SC to 1.0 mg/kg SC doses of efalizumab compared with 30.0% of the group who received 1.0 mg/kg to 2.0 mg/kg doses of efalizumab (no *P* values were reported for the doses). Of the group who received the dose escalation between 0.5 mg/kg and 1.0 mg/kg, 10.0% received an "excellent" or "better" rating for PGA (indicating ≥75.0% improvement from baseline) compared with 21.0% of patients in the dose escalation group who received between 1.0 mg/kg and 2.0 mg/kg of efalizumab.

Gottlieb *et al.* stated that there was no dose-dependent increase in adverse events. No statistical analyses were reported. They concluded that eight weekly doses of efalizumab produced clinically meaningful reduction in disease severity over 56 days.

5 LIMITATIONS OF CLINICAL REVIEW

For this CADTH report, patients with baseline BSA ≥10% and baseline PASI ≥10 were considered to have severe plaque psoriasis. Because there is no universal definition of severe plaque psoriasis, it can be debated that these criteria may reflect a broader population of patients with moderate to severe psoriasis. This is suggested by the discrepancies in how authors of the reports included in this CADTH report referred to the patient population in their studies.

The most common assessment measure for plaque psoriasis is the PASI. This commonly used instrument has been criticized.[8,10] PASI can be inaccurate in assessing the extent of the disease, and the risk of error in estimating the disease extent is compounded by the complexity in calculating the final score. In addition, there is no universal PASI score that represents treatment success. The most commonly used primary endpoint in the literature is PASI 75, but there is evidence that achieving PASI 50 is clinically meaningful.[10] PASI 50 is controversial, however, because it is not widely accepted by the European Medicines Evaluation Agency.[11]

Another criticism of the PASI is that it does not necessarily reflect how the disease affects a patient's QoL. Thus, it is important to address this through other measures such as the DLQI to obtain a more accurate understanding of a treatment's effectiveness. Lastly, the PASI is not routinely administered by clinicians, and thus, using it as a measurement of success may lack generalizability to clinical practice.[10]

Given the lack of high-quality evidence and the lack of evidence from comparative (head-to-head) trials (or indirect comparisons) comparing the efficacy of TIMs for the treatment of severe plaque psoriasis, it is not possible to determine which TIM provides the most efficacious, effective, and safe method of treatment. Gathering evidence on the efficacy of a TIM compared to a placebo does not necessarily provide the evidence required by health decision-makers as to which TIM(s) to fund. In addition, there is a paucity of trials (randomized or non-randomized with control groups) that extend past 24 weeks. There is likely to be information about longer term harm in non-controlled studies (e.g., case series). It is, however, beyond the scope of this report to include such studies. Furthermore, non-controlled studies such as case series lack the rigour necessary for strong conclusions to be made, because these studies are subject to potential biases that are not seen (or seen to a lesser extent) in studies with designs that reflect higher levels of evidence. Without these longer term data, an evaluation of the TIMs is limited for clinical effectiveness and harm.

3. What is comparative cost-effectiveness of adalimumab, alefacept, efalizumab, etanercept, and infliximab for treatment of patients with severe plaque psoriasis?

Two types of studies were selected in this review: studies in which the costs and effectiveness of at least two TIMS (economic evaluations) were estimated and studies in which only the costs of ≥2 TIMs (costing studies) were estimated. The methods and results from each selected costing study were reviewed and summarized in one paragraph. The review of the selected economic evaluation studies was more extensive. The methods of each economic study were assessed using the *British Medical Journal* (BMJ) checklist.[37,38] For each economic evaluation, a summary of the study background, methods, and results is provided. For most cost-effectiveness studies, tables of results are also provided. Some studies included costs and cost-effectiveness results for non-TIM treatments. Cost and cost-effectiveness results for the non-TIM treatments are excluded in the study summaries.

5.1 Review of costing studies

Five costing studies were selected from the literature search and reviewed.

Fisher[39] provided a sample of annual costs of treatments for severe psoriasis. These included estimates of annual costs for alefacept, efalizumab, and etanercept. Annual costs included the cost of medication only. Medication acquisition costs were derived from drugstore.com. Costs were expressed in US dollars. The year from which the costs were based was unspecified. The dosing regimens that were used to calculate annual costs were based on the approved or published doses for each drug. The drugs evaluated in the study and their corresponding assumed dosing regimens were for alefacept [15 mg IM or 7.5 mg IV bolus administered once weekly for 12 weeks (average of 1.5 of the above treatments per year)], for efalizumab [initial dose of 0.7 mg/kg SC followed by 1 mg/kg/week (maximum 200 mg/dose)], and for etanercept (50 mg twice weekly for three months then 50 mg SC once weekly). The annual cost of alefacept, efalizumab, and etanercept were estimated to be $17,910, $18,728, and $21,120 respectively.

In a study focusing on the use of phototherapy in severe psoriasis, Yelverton *et al.*[40] estimated the 30-year treatment cost of several TIMs. Annual costs included those related to medications and laboratory services, with annual follow-up. The dosing regimen that was assumed for each drug was 15 mg IM × 18 treatments/year for alefacept, 75 mg SC weekly for efalizumab, and 50 mg SC weekly for etanercept. The authors did not state the assumptions about drug administration setting or the frequency of follow-up. Medication acquisition costs were based on 2002 average wholesale prices. Other costs were derived from allowable Medicare expenses in North Carolina. The costs were expressed in 2002 US dollars. An annual 5.0% discount was used to calculate the 30-year treatment costs. The 30-year cost of efalizumab treatment was estimated to be $171,915. The 30-year costs were estimated to be $257,694 and $319,356 for etanercept and alefacept respectively.

Stein *et al.*[41] estimated the annual costs of moderate to severe psoriasis treatment with efalizumab, alefacept, etanercept, infliximab, and adalimumab. The costs included were those related to medications, visits to a physician's office, laboratory tests, and infusions. Eight annual visits to a physician's office were assumed for etanercept and adalimumab; six were assumed for the other TIMs. Assumptions for annual laboratory tests were six complete blood counts (CBCs) with efalizumab treatment, 18 cluster of differentiation 4 (CD4) counts with alefacept treatment, and one purified protein derivative for all other treatments. In addition, one chest x-ray per year was assumed for infliximab therapy. All IV infusions were assumed to occur at the physician's office. Patients were assumed to weigh 80 kg. Drug acquisition costs were obtained from the 2004 Drug Topics Red Book. Other costs were derived from the 2004 Medicare fee schedule. The costs were expressed in 2004 US dollars. The annual cost of treatment with etanercept was estimated to be $17,700 assuming a dosing regimen of 25 mg twice weekly and $34,800 assuming 50 mg twice weekly. The annual cost of alefacept was estimated to be $16,600 for IV (7.5 mg IV × 18 infusions) and $19,500 for IM (15 mg IM × 18 injections) dosing. The annual cost for infliximab based on six infusions of 5 mg/kg was estimated to be $17,700 and $34,800 based on six infusions of 10 mg/kg. Treatment with adalimumab was estimated to cost $34,800 assuming a regimen of 40 mg weekly and $17,700 assuming a regimen of 40 mg every other week.

Simpson *et al.*[40] estimated annual patients' out-of pocket costs and annual managed care organization's (MCO) costs for moderate to severe psoriasis treatment with several TIMs. Out-of-pocket costs included co-payments made by patients for visits to the physician and for pharmacy purchases. The third-party payer's costs (i.e., MCO) included those related to medications and visits to the physician's office. Medication acquisition costs were based on 2005 Drug Topics Red Book average wholesale values. The cost per visit to the physician's office was based on average Medicare reimbursement rates in North Carolina. The costs were expressed in 2005 US dollars. Annual out-of-pocket costs were estimated to be $840 for etanercept (50 mg SC × 60 injections/year),

Table 2: Cost per treatment success[43]			
Drug	**Annual Cost ($)**	**% Treatment Success**	**Cost/Treatment Success ($)**
alefacept 15 mg IM × 18 injections	16,000 to 20,000	40.0	40,600
etanercept 25 mg SC weekly	16,900	47.0	35,900
infliximab 5 mg/kg IV × 6 infusions	18,000	80.0	22,500

IM=intramuscular; sc=subcutaneous.

$405 for alefacept (15 mg IM × 18 injections/year), and $600 for efalizumab (15 mg SC × 52 injections/year). Etanercept was assumed to be associated with two extra office visits compared with the other TIMs analyzed. The duration of alefacept treatment was assumed to be 12 weeks, while the duration of treatment with the other TIMS was 52 weeks. The authors did not state the setting assumed for the administration of the medications. The third party payer's annual treatment costs were estimated to be $20,180 for etanercept, $17,817 for alefacept, and $18,290 for efalizumab.

Braun *et al.*[42] estimated the costs of TIMs in Germany for several indications including moderate to severe psoriasis. Treatment costs included the costs of medications only. Medication acquisition costs were derived from the Roten Liste 2006. The costs are presented in euros. The authors estimated the annual cost of adalimumab to be €22,269 for 40 mg SC every two weeks and €44,538 for 40 mg SC every week. The annual cost of psoriasis treatment with etanercept (2 × 25 mg/week for 12 weeks then 50 mg/week) was estimated to be €22,256. Estimates of the annual treatment cost with infliximab ranged from €10,589 to €35,309 depending on the drug regimen (3 mg/kg every eight weeks, 3 mg/kg every six weeks, 4 mg/kg every eight weeks, 5 mg/kg every eight weeks, and 5 mg/kg every six weeks) and weight of the patient (<67 kg to >100 kg).

5.2 Review of economic evaluations

Seven studies that included an economic evaluation were identified during the search strategy and reviewed. Results of the completed BMJ checklist for each study appear in Appendix 4.

Feldman *et al.*[43] estimated the cost-effectiveness of several treatments for severe psoriasis: etanercept 25 mg SC weekly, alefacept 15 mg IM × 18 injections, and infliximab 5 mg/kg IV × 6 infusions. The cost-effectiveness was estimated in terms of the cost per "treatment success," which was defined as having achieved PASI 75. The authors estimated the annual costs of each treatment from a third-party payer perspective. The costs included those related to medications, visits to the physician, nursing visits, and laboratory tests. Eight annual visits to the physician's office were assumed for etanercept, while six annual visits to the physician's office were assumed for infliximab and alefacept. The assumptions for annual laboratory tests included 18 CD4 counts with alefacept treatment and one purified protein derivative for etanercept and infliximab. In addition, one chest x-ray per year was assumed for infliximab therapy. All IV infusions were assumed to occur at the physician's office. Patients were assumed to weigh 75 kg. Drug acquisition costs were derived from the 2002 Drug Topics Red Book. The physician's and nursing office costs were based on the 2002 Medicare fee schedule. Laboratory costs were based on the 2002 Medicare laboratory fee schedule. The costs were in 2002 US dollars. The proportion of patients having treatment success for each TIM was estimated through a literature review. No details about the review are provided. The authors did not specify at what point the "treatment success" data were reported in the clinical studies.

Estimates of the annual costs, percentage of patients achieving treatment success, and average cost per treatment success for the TIMs

Table 3: Annual cost, per cent change in PASI, and average cost-effectiveness ratios for TIMs[44]

Treatment	Annualized Cost of Care	% PASI change	Cost per year/ PASI 50 ($)	Cost per year/ PASI 75 ($)
infliximab 5 mg/kg IM × 9 injections	26,436	82.8	15,964	23,946
etanercept 50 mg SC twice a week for 12 weeks, 25 mg twice a week for 40 weeks	21,158	64.2	16,478	24,717
efalizumab 1 mg/kg per week	17,999	52.0	17,307	25,960
alefacept 15 mg IV × 24 infusions	27,098	45.0	30,109	45,163

IM=intramuscular; IV=intravenous; PASI=Psoriasis Area and Severity Index; SC=subcutaneous.

analyzed in the study appear in Table 2. The cost per treatment success was estimated to be $40,600 for alefacept, $35,900 for etanercept, and $22,500 for infliximab. The authors note that infliximab was "relatively less costly" when cost per success was used. This assessment, however, was based on average cost-effectiveness ratios. The authors observed that infliximab had the lowest average cost-effectiveness ratio. No incremental analyses between the TIMs were undertaken.

Hankin *et al.* [44] compared the efficacy and the cost-effectiveness of phototherapy, oral systemic agents, and TIMs for moderate to severe psoriasis. The TIMs that were included in the analysis were alefacept, efalizumab, etanercept, and infliximab. Two cost-effectiveness measures were used in the analysis: cost per PASI 50 and cost per PASI 75. The annual costs that were estimated for each treatment included those related to medications, monitoring of patients, and treatment for adverse events. The annual dosing regimens for the TIMs were assumed to be 15 mg IV alefacept × 24 infusions; 1 mg/kg per week efalizumab; 50 mg SC etanercept twice a week for 12 weeks and 25 mg etanercept twice a week for 40 weeks; and 5 mg/kg IM infliximab × 9 injections.

IM and IV administrations were assumed to occur in a physician's office. Drug acquisition costs were based on the 2004 average wholesale price. The cost of monitoring for adverse events during each treatment was based on "recommended monitoring regimens" as specified on the product labels. The unit costs for monitoring were based on 2004 Medicare reimbursement rates. The source for the costs of treatment for adverse events was unspecified. The costs were expressed in 2004 US dollars.

The effectiveness measures were obtained from the literature. A formal systematic review was undertaken to identify studies that included one treatment of interest and had PASI as an outcome. Of 3,886 articles identified from their search, 16 met their inclusion criteria. A review of the literature was also undertaken to determine the risk of adverse events for each treatment. The authors did not provide details on how they pooled data from these studies. No statistical analysis of the effectiveness outcomes was provided. The authors did not specify at what point the PASI data were reported in the clinical studies. Table 3 presents the annual cost, per cent change in PASI, and average cost-effectiveness ratios for the TIMs included in the analysis. Based on the cost per PASI 50 outcome, the average cost-effectiveness was estimated to be $15,964 for infliximab, $16,478 for etanercept, $17,307 for efalizumab, and $30,109 for alefacept. Based on the cost per PASI 75 outcome, the average cost effectiveness was estimated to be $23,946 for infliximab, $24,714 for etanercept, $25,960 for efalizumab, and $45,163 for alefacept. A proper incremental cost-effectiveness analysis between the TIMs was not conducted. No conclusions about the cost-effectiveness among the TIMs were stated by the authors.

Table 4: Cost-effectiveness ratios for TIMs[46]			
Drug	**Efficacy**	**3-Month Cost (2003 US$)**	**Cost-Effectiveness ($)**
alefacept 15 mg IM × 12 injections	21.0%	13,393	63,776
efalizumab 1 mg/kg SC weekly	25.0%	4,299	17,196
etanercept 50 mg SC twice weekly	49.0%	7,993	16,312
infliximab 5 mg/kg IV × 3 infusions)	82.0%	8,774	10,700

IM=intramuscular; IV=intravenous; sc=subcutaneous; TIM=targeted immune modulator.

Miller and Feldman[45] present cost-effectiveness estimates for treatments of moderate to severe psoriasis.

The cost-effectiveness results from two published studies (Hankin *et al.*,[44] Feldman *et al.*[43]) are presented. In addition to these published average cost-effectiveness ratios, the authors estimate the cost per treatment success for adalimumab and efalizumab using the same methods that Feldman *et al.*[43] used. The annual dosing regimen that was assumed for etanercept was 50 mg SC twice weekly for three months, then 25 mg SC twice weekly. Two dosing regimens for adalimumab were investigated: 40 mg every other week and 40 mg every week. The authors do not state what year the costs were based on. The authors did not specify at what point the treatment success data were reported in the clinical studies.

The cost per treatment success with efalizumab was estimated to be $42,000. The cost per treatment success of adalimumab given every week was estimated to be $46,000, while the cost per treatment success of adalimumab given every other week was estimated to be $36,000. No incremental cost-effectiveness analyses between TIMs were presented. The authors did not provide disaggregated costs and treatment success estimates for each drug. Therefore, a table of cost-effectiveness results is not presented for this study. The authors did not provide conclusions on the relative cost-effectiveness among the TIMs.

Pearce *et al.*[46] examined the cost-effectiveness of treatments of moderate to severe psoriasis. Among the treatments analyzed were several TIMs (efalizumab, alefacept, infliximab, and etanercept). The cost-effectiveness is presented in terms of cost per PASI 75. A 12-week treatment cost model was created for each alternative. The costs included those related to medications, visits to a physician, and laboratory tests. The annual dosing regimens assumed were 15 mg alefacept IM × 12 injections, 1 mg/kg efalizumab SC weekly, 50 mg etanercept SC twice weekly, and 5 mg/kg infliximab IV × 3 infusions. Three visits to a physician's office were assumed for all TIMs. Patients who were treated with alefacept were assumed to require 12 CD4 counts. Three complete blood counts with differential (CDPs) were assumed for efalizumab, while one CDP was assumed for infliximab treatment. One chest x-ray was assumed for infliximab treatment. The costs were based on 2003 US dollars. The medication costs were based on the average wholesale prices from the 2003 Drug Topics Red Book. Other resource costs were based on Medicare reimbursement rates.

A formal review of PubMed was undertaken to identify RCTs that evaluated one treatment of interest and included PASI 75 as an outcome. Of 4,217 citations identified in their search, 13 met their inclusion criteria. When efficacy data were available from >1 study, data were pooled by weighting the study results by the sample size. No statistical analysis of the efficacy was provided. The PASI data were reported at approximately 12 weeks (range 10 to 14 weeks) in the clinical studies.

Table 4 presents the three-month costs, efficacy (PASI 75), and average cost-effectiveness ratios for the TIMs that were analyzed in the study. The cost per PASI 75 was estimated to be $63,776 for alefacept, $17,196 for efalizumab, $16,312 for etanercept, and $10,700 for infliximab. The authors did undertake a formal incremental cost-effectiveness analysis. Because non-TIM

Table 5: Cost-effectiveness ratios[47]						
Medication	**Dosage**	**Annual Cost ($)**	**% PASI 75**	**Mean DLQI Improvement**	**Cost per Patient Achieving PASI 75 ($)**	**Cost per Patient Achieving DLQI MID ($)**
alefacept	15 mg IM (12 injections)	20,376	21.0	4.9	74,625	27,136
efalizumab	1 mg/kg SC	18,214	28.0	5.6	18,200	5,277
efalizumab	2 mg/kg SC	36,050	28.0	NR	35,350	NA
etanercept	25 mg SC	8,849	14.0	5.8	20,236	2,109
etanercept	50 mg SC (2 × 25 mg SC/week)	17,402	33.0	7.0	13,827	3,289
etanercept	61.53 mg SC (2 × 50 mg SC/week for 12 weeks, then 50 mg SC/week)	21,349	49.0	7.5	17,600	6,073
infliximab	3 mg/kg IV (3 infusions)	13,245	72.0	8.8	9,768	5,019
infliximab	5 mg/kg IV (3 infusions)	17,395	84.0	10.3	10,896	5,389
infliximab	10 mg/kg IV (3 infusions)	33,993	73.0	NR	24,662	NA
adalimumab	40 mg SC every other week	17,402	53.0	NR	8,466	NA
adalimumab	40 mg SC once weekly	34,508	80.0	NR	10,652	NA

DLQI=Dermatology Life Quality Index; IM=intramuscular; IV=intravenous; NR=not reported; NA=not applicable; PASI=Psoriasis Area and Severity Index; SC=subcutaneous.

treatments were included in the analysis, however, the findings are not relevant.

Nelson *et al.*[47] estimated the cost-effectiveness of TIMs in patients with moderate to severe psoriasis in terms of two outcomes: the cost per patient achieving PASI 75 and the cost per patient achieving a clinically minimally important difference (MID) in the DLQI. The annual costs estimated for each TIM included medications, visits to a physician, and laboratory tests. The authors assumed that patients weighed an average of 80 kg. No details on the assumptions used regarding visits to a physician or laboratory tests were stated. The costs were based on 2004 US dollars. The medication costs were based on the average wholesale price from the 2004 Drug Topics Red Book. The costs of visits to a physician and laboratory testing were determined from the 2004 Medicare clinical laboratory fee schedule.

A search of PubMed was completed to identify RCTs that included the effectiveness outcomes of interest (PASI 75, DLQI). The authors identified 13 "suitable" RCTs with PASI 75 outcomes and six "suitable" RCTs with DLQI outcomes. The effectiveness measures for each TIM were estimated by means of the simple pooling of studies based on the number of patients. The statistical analysis of the effectiveness measures was not reported. The PASI 75 and DLQI data were reported at 12 weeks in the clinical studies.

Table 5 presents the annual costs, per cent of patients achieving PASI 75, mean DLQI improvement, with average cost-effectiveness ratios. For each TIM, various dosage

assumptions were made. Based on these results, the authors conclude that adalimumab and infliximab "appear" to be the most cost-effective TIMs. The conclusions are based on these agents having the lowest average cost-effectiveness ratio. The authors' conclusions are faulty on more than one level. First, relative cost-effectiveness between ≥2 treatments cannot be properly assessed using average ratios. Second, the average ratios were not calculated properly. For example, adalimumab 40 mg weekly was estimated to cost $34,211 with 80.0% of patients achieving PASI 75. This translates into an average cost per patient achieving PASI of $43,225. The authors, however, calculated the cost per PASI 75 as $10,652. The estimates appear to be erroneous for all comparators. A proper incremental cost-effectiveness analysis between the TIMs was not conducted.

Wanke *et al.*[48] measured the cost-effectiveness of TIMs (etanercept, efalizumab, alefacept). The cost-effectiveness was measured in terms of the cost per PASI 50 and the cost per PASI 75 for each treatment. The analysis was taken from a managed care perspective. Three-month costs for each treatment alternative were estimated. In addition to medication costs, physicians' fees, laboratory costs, and costs of adverse events were included. The authors report that drug prices were based on the "average wholesale price." Other resource costs were based on Medicare reimbursement rates and the MEDSTAT DRG Guide. Wanke does not report the year in which the costs were based on. The severity of psoriasis was not reported. The authors state that the efficacy measures (PASI 50, PASI 75) were based on "comparable clinical trials." No description of the methods around estimating efficacy is provided. Only an abstract of this study was available. Table 6 presents the three-month costs, rates of PASI 50, rates of PASI 75, and average cost-effectiveness ratios for the TIMs. The cost per PASI 50 was estimated to be $29,652 for alefacept 15 mg weekly, $8,408 for efalizumab 1 mg/kg weekly, $7,458 for etanercept 25 mg twice weekly, and $11,263 for etanercept 50 mg twice weekly. The cost per PASI 75 was estimated to be $59,304 for alefacept 15 mg weekly, $19,873 for efalizumab 1 mg/kg weekly, $12,723 for etanercept 25 mg twice weekly, and $17,010 for etanercept 50 mg twice weekly. Although the authors present average cost-effectiveness ratios, their conclusions were based on an incremental analysis. The authors concluded that etanercept 25 mg twice weekly was the most cost-efficacious treatment because it was less costly and more effective compared with alefacept and efalizumab. This conclusion, however, ignores the incremental cost-effectiveness of etanercept 25 mg compared with etanercept 50 mg.

Wollacott *et al.*[11] created an economic model to evaluate the cost-effectiveness of several systemic treatments, biologic treatments, and supportive care for patients with moderate to severe psoriasis. This was part of a health technology assessment of efalizumab and etanercept in the treatment of psoriasis. The base-case analysis included etanercept, efalizumab, and supportive care in the analysis. A sensitivity analysis also included infliximab with other systemic treatments.

Table 6: Cost-effectiveness results[48]

Treatment	3-Month Costs ($)	% PASI 50	% PASI 75	Cost per PASI 50 ($)	Cost per PASI 75 ($)
etanercept 25 mg twice weekly	4,326	0.58	0.34	7,458	12,723
etanercept 50 mg twice weekly	8,335	0.74	0.49	11,263	17,010
efalizumab 1 mg/kg weekly	4,372	52.0	22.0	8,408	19,873
alefacept 15 mg IM weekly	12,454	42.0	21.0	29,652	59,304

IM=intramuscular; PASI=Psoriasis Area and Severity Index.

Dosing for efalizumab was assumed to include an initial dose of 0.7 mg/kg, then weekly injections of 1.0 mg/kg. Dosing for infliximab was assumed to include three initial doses of 3 mg/kg to 5 mg/kg in the first six weeks then an infusion every eight weeks afterwards. Several dosing assumptions for etanercept were considered. It is difficult to ascertain the dosing regimens that were assumed. They appear to be 25 mg infusions twice a week for 12 weeks then 25 mg infusions every week; 25 mg infusions twice a week for 12 weeks; and 50 mg twice a week for 12 weeks. The effectiveness measure used in the model was the quality-adjusted life-year (QALY). The perspective of the analysis was that of a third-party payer. The time horizon used in the model is unclear. It appears to be 10 years.

The costs of medications, administration, monitoring, outpatient visits, and inpatient stays were included in the analysis. The length of stay for an inpatient admission was based on the Department of Health Hospital Episode statistics (2002/2003). The authors assumed that educating patients to self-inject with efalizumab or etanercept would require three one-hour sessions with a nurse. For infliximab, it was assumed that two hours of monitoring by a nurse would be needed for the first four infusions, with one hour of monitoring required for subsequent infusions. This assumption was based on the British Society of Rheumatology's guidelines. Experts' opinion was used for other resource use assumptions. The drug costs were derived from the 2004 British National Formulary 48 and from the manufacturer of efalizumab. Outpatient costs were based on the National Health Service Reference cost category J10op. The cost of an infusion visit was based on the National Health Service Reference cost category J09op. Costs are reported in 2003-2004 UK pounds.

QALYs were estimated for each treatment based on the proportion of patients achieving PASI 50, PASI 75, and PASI 90. These proportions were derived from a mixed comparison meta-analysis completed as part of the clinical chapter of the health technology assessment. The clinical data (PASI) was based on 12-week data from the clinical trials for etanercept and efalizumab. The authors did not state the duration of treatment for the data used for infliximab. The utility values associated with each PASI level were derived by the authors using data from "the three etanercept trials and the HODaR Database (http://www.hodar.co.uk/)." The trial data were used to map the relationship in the change in DLQI with different PASI levels achieved after treatment. The HODaR included patients who completed DLQI and EQ-5D questionnaires. It was used to estimate the relationship between DLQI and utility values.

Table 7 provides the cost-effectiveness results for the various TIMs that were investigated. The costs and QALYs presented for each strategy represents the costs and QALYs incremental to those for a supportive care strategy, as this is the manner in which the authors provided the results. Etanercept 25 mg twice a week for 12 weeks had the lowest costs associated with it while etanercept 50 mg twice a week for 12 weeks had the highest costs (Table 7). Infliximab was estimated to have the highest number of expected QALYs. Etanercept 25 mg twice a week for 12 weeks is less costly and has more (or equal) QALYS than efalizumab and etanercept 25 mg twice weekly continuous treatment and therefore dominates these strategies. Infliximab dominates (lower costs, higher QALYs) compared with etanercept 50 mg twice a week for 12 weeks. There is a tradeoff between costs and QALYs between etanercept 25 mg twice a week for 12 weeks and infliximab. The authors provide cost-effectiveness ratios of each strategy compared with a supportive care strategy (Table 7). The authors do conduct a proper incremental multi-comparator analysis; however, because it includes non-TIM strategies, the results are not relevant for this review.

6 LIMITATIONS OF ECONOMIC REVIEW

Our review of the costing studies did not identify any Canadian studies. The studies that investigated the one-year US treatment cost of psoriasis treatment provided consistent estimates of the costs of TIMs.

Table 7: Cost-effectiveness results[11]				
Medication	**Dosage**	**Incremental Costs (£)**	**Incremental QALYs**	**ICER Versus Supportive Care (£)**
supportive care	NA	0	0	-
etanercept	25 mg twice a week for 12 weeks	3,415	0.116	29,451
efalizumab	1 mg/kg SC	5,232	0.112	46,893
etanercept	25 mg twice a week continuously	5,337	0.116	46,025
infliximab	3 mg/kg to 5 mg/kg three times in the first 6 weeks and once every 8 weeks thereafter	6,918	0.134	51,748
etanercept	50 mg twice a week for 12 weeks	10,258	0.123	83,477

ICER=incremental cost-effectiveness ratio; NA=not applicable; QALY=quality-adjusted life-year; SC=subcutaneous.

The estimates of annual costs with alefacept ranged from $16,000 to $17,910. Efalizumab cost estimates ranged from $18,290 to $19,728. Etanercept cost estimates ranged from $17,700 to $34,800. The variation in these estimates is due to different assumptions about dosing regimens. One costing study estimated the one-year cost of infliximab ($17,700 5 mg/kg dosing; $34,300 10 mg/kg dosing) and adalimumab ($17,700 40 mg every other week; $34,800 40 mg every week).

The published literature offers limited insight into the relative cost-effectiveness between the TIMs for the treatment of severe psoriasis in Canada. None of the cost-effectiveness analyses was conducted from a Canadian perspective. In addition, there are problematic methodological issues that are common to the studies. First, most of the studies did not conduct a proper multi-comparator cost-effectiveness analysis. Such analysis involves determining which treatment strategies are dominated (more costly, less effective) by other strategies, then calculating the incremental cost-effectiveness of moving from one non-dominated treatment to a more effective but more costly non-dominated treatment. The determination of which treatment strategy is cost-effective then depends on how much one is willing to pay for the incremental effectiveness. Proper conclusions on cost-effectiveness cannot be made using average ratios as was done in nearly all the cost-effectiveness studies being reviewed.

Only Woolacott *et al.*'s study used QALYs as the outcome. Although the PASI score may be an accepted measure for efficacy, having only a disease-specific outcome in cost-effectiveness analyses limits the comparability of cost-effectiveness results to common $/QALY benchmarks or to cost-effectiveness found in other disease areas. In addition, all but one cost-effectiveness study were limited to one year despite the fact that severe psoriasis is a chronic disease with negative impacts on QoL. This highlights the need for a Canadian cost-effectiveness analysis of TIMs for the treatment of severe plaque psoriasis in adult patients.

4. What is budget impact of funding treatment with adalimumab, alefacept, efalizumab, etanercept, or infliximab for one year for all Canadian adults with severe plaque psoriasis?

Table 5 Appendix 5 presents the base-case estimates of the number of Canadian adults treated for severe plaque psoriasis and the annual treatment cost for Canada broken down by province. We estimate that 1,355 Canadians on public drug plans will be treated for severe plaque psoriasis (Table 5) resulting in a Canada-wide annual treatment cost of $30.1 million. It is estimated that Ontario, Québec, and British Columbia have the highest annual treatment costs ($12.0 million, $7.2 million, and $4.1 million respectively).

Table 6 presents several sensitivity analyses to reflect the uncertainty around some of the assumptions used in the BIA. If the prevalence of psoriasis is assumed to be 1% (instead of 1.5% in the base-case analysis) (Table 6), the annual treatment cost for public drug plans in Canada becomes $20.1 million, while a 2.0% prevalence rate translates to a total annual treatment cost of $40.1 million.

In the base-case analysis, it was assumed that 23.0% of severe plaque psoriasis patients taking oral systemic medications would move to treatment with a TIM. If this percentage is assumed to be 16.0% (Table 6), the annual treatment cost is $20.9 million. If this percentage is 30.0%, the annual treatment cost estimate becomes $39.3 million.

In the base case, it was assumed that 4.0% of all patients treated in a given year would be receiving induction therapy with a TIM. This percentage was also varied in the sensitivity analysis. If it is assumed that 0.0% patients are in their first year of treatment, the annual treatment cost estimate becomes $29.8 million. If it is assumed that 100.0% of patients are in their first year of treatment, the annual treatment cost is estimated to be $36 million.

In the base-case analysis, it was assumed that the average weight of psoriasis patients is 90 kg. If the average weight is assumed to be 80 kg, the annual treatment cost is estimated to be $29.2 million. If the average weight is assumed to be 100 kg, the annual treatment cost estimate becomes $31.0 million.

7 CONCLUSIONS AND IMPLICATIONS FOR DECISION AND POLICY MAKING

Because of the non-existence of comparative trials or meta-analyses using indirect comparisons, no comparative conclusions can be made regarding the relative efficacy of TIMs for the treatment of adults with severe plaque psoriasis.

Each TIM therapy resulted in between 14.0% and 87.9 % of patients achieving a PASI 75 in the short term (up to 24 weeks). It is unclear, however, how this endpoint translates clinically. On the other hand, DLQI and PGA sores, when reported, were also consistently shown to improve after TIM therapy. Thus, these commonly used outcome measures all agree in the direction of therapeutic effect, i.e., the literature consistently suggests that the physical aspects of the disease and patient-rated QoL improve for a sizeable portion of the adult patient population who are treated with TIMs.

No conclusions regarding adverse events associated with TIMs for periods longer than one year could be made because the information retrieved was limited to one HTA and one SR, neither of which reported statistical information on adverse events. Adverse events are often not reported well in RCTs, and this is complicated when the incidences of adverse events are rare, as is in the case of TIMs. Therefore, it cannot be easily determined whether adverse events are attributable to TIM therapy, plaque psoriasis, or chance. Advisory warnings regarding treatment with adalimumab, alefacept, efalizumab, etanercept, and infliximab have come from Canadian and international organizations. Since 2000, there have been 24 advisories about the use of TIMs in adults. The most common warnings were regarding opportunistic infection (especially tuberculosis), malignancies, and hepatitis B reactivation. All three were noted for adalimumab, etanercept, and infliximab. More information about these warnings is presented in Appendix 3 Table 1.

No included report provided statistical analyses on the dosing therapies of adalimumab, alefacept, or efalizumab. Limited evidence was found on the dosing of infliximab and etanercept therapy. No advantage to any dosing regimen for these two therapies emerged in the literature. Some evidence was found suggesting that a continuous (e.g., every eight weeks) maintenance therapy, as opposed to an “as

needed" maintenance therapy, may be more effective with infliximab. For patients taking etanercept, there was some evidence to suggest that providing continuous maintenance therapy resulted in more patients achieving or maintaining a "clear" or "almost clear" score (0, 1, or 2) on the PGA. No RCT reported *P* values for the different dosing regimens. Thus, no conclusions about the observed differences in rates of adverse events could be made. All dosing regimens, however, resulted in significant differences in reported clinical outcomes when compared with placebo. In addition, there were no *P* values reported for the incidence of patients taking different dosing regimens. Therefore, it is unclear whether there is a dose-dependent association with any adverse event(s).

Based on available clinical evidence and given the absence of comparative trials, it is not possible to suggest that any one TIM is more efficacious than another. The TIMs differ in terms of mode of action and mode of administration, complicating meaningful comparisons of clinical effectiveness. In addition, longer term (>24 weeks) data from well-designed, controlled, comparative studies are needed to assess the efficacy, effectiveness, and harm in patients with severe plaque psoriasis. No literature was retrieved on adalimumab therapy for the off-label indication of plaque psoriasis.

The Canadian annual cost of treating severe plaque psoriasis patients with a TIM was estimated to be $30.1 million. This estimate was sensitive to assumptions on Canadian psoriasis prevalence rates and on assumptions about the proportion of patients taking an oral systemic who would transfer to treatment with a TIM. The budget impact analysis was based on standard recommended dosing regimens and did not take possible "dose creep" into account for any TIM. Given the potential budget impact of funding TIMs for severe plaque psoriasis, comparative information on the long-term benefits, harms, and cost-effectiveness of these agents should be gathered to support funding decisions.

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APPENDIX 1

Table 1: Dosing, mechanism of action, and Notice of Compliance information on adalimumab, alefacept, efalizumab, etanercept, and infliximab

Mechanism of Action	Dosing	Health Canada, Notice of Compliance (year-month-day)
adalimumab[19]*		
binds to TNF-α and blocks its interaction with cell surface TNF receptors	40 mg SC every other week; clinical response expected within 12 weeks	2004-09-24[49]
alefacept[16]		
inhibits T-cell activation, induces apoptosis of memory-effector T-cells	15 mg IM once a week; course of up to 12 injections over 12 week period; intermittent re-treatment with subsequent courses may be initiated as needed	2004-10-06[50]
efalizumab[15]		
interferes with T lymphocytes' adhesion to other cell types	initial single 0.7 mg/kg body weight by IV followed by weekly injections of 1.0 mg/kg body weight; maximum single dose should not exceed total of 200 mg	2005-10-24[51]
etanercept[17]		
binds to soluble and cell surface TNF and blocks its interaction with cell surface TNF receptors	50 mg twice a week SC, which can be given with 50 mg single-use prefilled syringe or SureClick autoinjector; 50 mg dose can also be given as two 25 mg SC injections with multiple-use vials; when given as 2 injections, injections should be given on same day once weekly or 3 to 4 days apart	2000-12-01[52]
infliximab[18]		
neutralizes biological activity of TNF-α by binding with TNF-α, thus inhibiting binding of TNF-α with its receptors	5 mg/kg IV at 0, 2, and 6 weeks, then every 8 weeks thereafter; stop treatment if response is inadequate at week 14, after infusions at weeks 0, 2, and 6	2001-06-06[53]

*Adalimumab is not currently indicated for plaque psoriasis. Dosing information pertaining to adalimumab is for patients with psoriatic arthritis. IM=intramuscular; IV=intravenous; SC=subcutaneous; TNF=tumour necrosis factor.

APPENDIX 2

Awaiting translation

HTA or SR

1. TNF-α inhibitors and efalizumab for the treatment of skin diseases.[54] Norwegian Knowledge Centre for the Health Services, 2007.

   This review assessed 26 publications (RCTs and RCT follow-up studies), of which 24 pertained to moderate to severe psoriasis, and four of which were health economic evaluations (three from the US and one from the UK). This SR did not identify any studies that compared TNF-α or efalizumab with each other. The language was Norwegian.

2. Efalizumab for psoriasis: A systematic review. [55] Chen *et al*. *Chinese Journal of Evidence-Based Medicine*, 2006

   This SR included three RCTs (total of 1,651 adult patients with moderate to severe plaque psoriasis). Based on the accompanying abstract (which was published in English), the authors noted that the RCTs were of high methodological quality. Efalizumab was given at a dose of 1 mg/kg/week or 2 mg/kg/week and was compared with placebo. At week 12, the pooled analyses indicated that both doses of efalizumab were equally effective (P <0.05), compared with placebo, in terms of PASI 50, PASI 75, and PASI 90. No serious adverse events were identified. The authors concluded that efalizumab treatment for 12 weeks was safe and effective for treating adult patients with moderate to severe plaque psoriasis. The language was Chinese.

3. The role of biological drugs in the treatment of psoriasis, results from 9 randomized, placebo-controlled trials.[56] Kemény *et al.*

   It is unclear whether this was a true systematic review and meta-analysis because the methods section only mentioned that the authors searched Medline. The authors combined data from 4,165 patients in 13 trials. The authors concluded that the TIMS studied are statistically more likely to result in PASI 75 when compared with placebo. The language was Hungarian.

RCT

4. Remicade in moderate to severe plaque psoriasis.[57] Ortonne, 2006.

   This report compared infliximab versus placebo in a doubled blinded, cross-over trial. It appeared that data were collected up to week 66, but it was unclear whether QoL or adverse event data were reported past week 50. It is also unclear whether the data past 52 weeks contained a control (placebo) group or whether all patients were receiving infliximab by that time. The language was French.

Not completed or in progress

1. A systematic review of the clinical effectiveness, safety, tolerability, and cost-effectiveness of efalizumab and etanercept within their licensed indications for the treatment of psoriasis.[58] National Coordinating Centre for Health Technology Assessment, 2007; a Cochrane review is being undertaken by NICE.

A request was made to the author to provide a project release date. No reply from the author was received.

2. Infliximab for the treatment of adults with psoriasis – Final scope. National Institute for Health and Clinical Excellence. October 2006.[59]

   The aim of this report is to provide a clinical and cost-effectiveness report on infliximab for the treatment of psoriasis and to provide guidance to the NHS for England and Wales.

3. Biologics for chronic plaque psoriasis (protocol).[60] A Cochrane protocol published by Angus *et al.*, 2006.

   This protocol aims to assess the RCTs that evaluate the efficacy and safety of biologic therapy for plaque psoriasis. No mention is made of whether the systematic review will report separately the findings for patients with moderate to severe psoriasis. The primary outcomes are global assessment of improvement, duration of response, and improvement of QoL. Secondary outcomes are PASI or PGA if PASI is unavailable and delayed response to treatment.

No access to full study

1. Off-label uses for tumour necrosis factor inhibitors in ankylosing spondylitis, ulcerative colitis, and psoriasis.[61] Blue Cross Blue Shield Association, Technology Evaluation Center, 2003

   This report summarizes the evidence on infliximab and etanercept for chronic psoriasis. No reports were found on adalimumab. The conclusion was that there was insufficient evidence to permit conclusions about the clinical effectiveness of these three TIMS. Furthermore, as the clinical effectiveness of infliximab, adalimumab, and etancercept is yet to be determined in an investigational setting, it cannot be determined whether there is improvement outside an investigational setting.

APPENDIX 3

Table 1: Summary of advisories on alefacept, efalizumab, etanercept, infliximab, and adalimumab

Warning Type	Year	Reason(s) for Warning
Adalimumab		
prescribing information – addition of information[62]	2007	risk of serious infection
		warnings and precautions – serious infections, malignancies, hepatitis B reactivation, immunizations
		adverse reactions
		drug interactions – live vaccines
		patient counselling information
package insert – addition of information[63]	2006	box warning – risk of infection (TB)
Adverse Drug Reactions Bulletin[64]	2006	hypersensitivity reactions – immediately post-injection or delayed
		serious and life-threatening infection and sepsis; recrudescence of tuberculosis and other granulomatous diseases
		reactivation of hepatitis B
		malignancy, including lymphoma
		hematological reactions such as pancytopenia and aplastic anemia
		autoimmunity – e.g., drug-induced lupus
		CNS reactions, including demyelinating disorders and seizures
		new-onset heart failure or worsening of advanced heart failure
Dear Dr. letter[65]	2006	hepatitis B reactivation
FDA Patient Safety News[66]	2005	warning – lymphoma risk with TNF blockers
FDA Patient Safety News[66]	2005	warning – lymphoma risk with TNF blockers
patient information – addition of information[67]	2005	warning – serious infections
		warning – neurologic events
		warning – malignancies
Dear Dr. letter[68]	2004	prescribing adalimumab with anakinra – not recommended
MedWatch notice of letter[69]	2004	prescribing adalimumab with anakinra – not recommended
patient information[70]	2004	increased risk of TB
Alefacept		
patient information – addition of information[71]	2005	contraindications – patients with HIV
patient information – addition of information[72]	2003	warning – lymphopenia
Efalizumab		
Dear Dr. letter[73]	2005	immune-mediated hemolytic anemia
		thrombocytopenia and serious infection
MedWatch notice of letter[74]	2005	immune-mediated hemolytic anemia
		thrombocytopenia and serious infection
patient information – addition of information[75]	2005	warnings – serious infections, immune-mediated thrombocytopenia, immune-mediated hemolytic anemia, psoriasis worsening, and variants
		precautions – arthritis events
		information for patients – pregnancy, post-marketing experience

Etanercept		
Adverse Drug Reactions Bulletin[64]	2006	hypersensitivity reactions – immediately post-injection or delayed
		serious and life-threatening infection and sepsis; recrudescence of tuberculosis and other granulomatous diseases
		reactivation of hepatitis B
		malignancy, including lymphoma
		hematological reactions such as pancytopenia and aplastic anemia
		autoimmunity – e.g., drug-induced lupus
		CNS reactions, including demyelinating disorders and seizures
		new-onset heart failure or worsening of advanced heart failure
Dear Dr. letter[65]	2006	hepatitis B reactivation
FDA Patient Safety News[66]	2005	warning on lymphoma risk with TNF blockers
FDA Patient Safety News[66]	2005	warning on lymphoma risk with TNF blockers
prescribing information – addition of information[76]	2005	warnings – malignancies
		precautions – drug interactions (patients with Wegner's granulomatosis)
		adverse reactions – malignancies
warning letter re: advertising[77]	2005	television advertisement overstates effectiveness of etanercept
Dear Dr. letter[78]	2002	prescribing etanercept with anakinra – not recommended/risk of infection
Infliximab		
Adverse Drug Reactions Bulletin[64]	2006	hypersensitivity reactions – immediately post-injection or delayed
		serious and life-threatening infection and sepsis
		recrudescence of tuberculosis and other granulomatous diseases
		reactivation of hepatitis B
		malignancy, including lymphoma
		hematological reactions such as pancytopenia and aplastic anemia
		autoimmunity – e.g., drug-induced lupus
		CNS reactions, including demyelinating disorders and seizures
		new-onset heart failure or worsening of advanced heart failure
Dear Dr. letter[65]	2006	hepatitis B reactivation
FDA Patient Safety News[66]	2005	warning – lymphoma risk with TNF blockers
FDA Patient Safety News[66]	2005	warning – lymphoma risk with TNF blockers
package insert – addition of information[79]	2005	precautions – geriatric use
		adverse reactions – infections; hepatotoxicity
		addition of patient information sheet
Dear Dr. letter[80]	2004	risk of malignancies
Dear Dr. letter[81]	2004	hepatotoxicity
		increased risk of infection
MedWatch notice of letter[82]	2004	increased risk of malignancies
Dear Dr. letter[83]	2001	higher mortality and hospitalization in patients with congestive heart failure
urgent safety restriction[84]	2000	increased risk of TB or other opportunistic infections

CNS=central nervous system; FDA=Food and Drug Administration; HIV=human immunodeficiency virus; TB=tuberculosis, TNF=tumour necrosis factor.

APPENDIX 4

Table 1: BMJ checklist for economic reviews results							
Study Design	**Feldman et al.[43]**	**Hankin et al.[44]**	**Miller et al.[45]**	**Pearce et al.[46]**	**Nelson et al.[47]**	**Wanke et al.[48]**	**Wollacott et al.[11]**
research question stated	√	√	√	√	√	NA	√
economic importance of research question stated	no	√	√	√	no	NA	√
viewpoint(s) of analysis clearly stated and justified	no	√	no	√	no	NA	no
rationale for choosing alternative programs or interventions compared stated	√	√	√	√	√	NA	√
alternatives being compared clearly described	no	no	√	√	√	√	√
form of economic evaluation used stated	√	√	√	√	√	√	√
choice of economic evaluation justified in relation to questions addressed	√	√	√	no	no	NA	√
Data Collection							
source(s) of effectiveness estimates used stated	√	√	√	√	no	√	√
details of design and results of effectiveness study given (if based on 1 study)	√	√	√	√	√	NA	√
details of method of synthesis or meta-analysis of estimates given (if based on overview of effectiveness studies)	√	√	√	no	no	NA	√
primary outcome measure(s) for economic evaluation stated	√	√	√	√	√	√	√
methods to value health stated and other benefits stated	NA	NA	√	√	NA	NA	√
details of subjects from whom valuations obtained given	√	no	√	√	no	NA	√
productivity changes (if included) reported separately	NA	NA	NA	NA	NA	NA	NA
relevance of productivity changes to study question discussed	NA	NA	NA	NA	NA	NA	NA
quantities of resources reported separately from unit costs	√	√	no	√	no	NA	√

Table 1: BMJ checklist for economic reviews results							
Study Design	**Feldman et al.[43]**	**Hankin et al.[44]**	**Miller et al.[45]**	**Pearce et al.[46]**	**Nelson et al.[47]**	**Wanke et al.[48]**	**Wollacott et al.[11]**
methods for estimation of quantities and unit costs described	√	√	no	√	√	NA	√
currency and price data recorded	√	√	√	√	√	NA	√
details of price adjustments for inflation or currency conversion given	NA	no	no	√	NA	NA	√
details of model used given	√	NA	√	NA	√	NA	√
choice of model used and key parameters on which it is based justified	√	NA	√	√	no	NA	√
Analysis and Interpretation of Results							
time horizon of costs and benefits stated	√	√	√	NA	√	√	no
discount rate(s) stated	NA	no	no	NA	no	NA	√
choice of rate(s) justified	NA	no	no	NA	no	NA	√
explanation given if costs or benefits not discounted	no	no	no	no	no	no	NA
statistical test and confidence intervals given for stochastic data	√	no	no	no	no	no	√
approach to sensitivity analysis given	√	no	no	no	no	NA	√
choice of variables for sensitivity analysis justified	√	no	no	no	no	NA	√
ranges over which variables varied stated	√	no	no	no	no	NA	√
relevant alternatives compared	√	√	√	√	√	NA	√
incremental analysis reported	√	no	no	√	no	√	√
major outcomes presented in disaggregated and aggregated forms	no	√	no	√	√	NA	√
answer to study question given	√	√	√	√	√	NA	√
conclusions follow from data reported	√	√	√	√	√	NA	
conclusions accompanied by appropriate caveats	√	√	√	√	√	NA	√
sum of "no" and "not clears"	11	11	13	7	16	30	2

BMJ=*British Medical Journal,* NA=not applicable..

APPENDIX 5

Budget Impact Analysis Calculations

Table 1: Calculation of proportion of adult population who will be treated with TIMs for severe plaque psoriasis	
Component	**Proportion**
a) proportion of population with psoriasis	0.015
b) proportion of psoriasis that is plaque psoriasis	0.85
c) proportion of plaque psoriasis that is severe	0.25
d) proportion of severe plaque psoriasis patients that take oral systemic medications	0.18
e) proportion of severe plaque psoriasis patients on systemic therapy that will be treated with TIM	0.23
proportion of population treated with TIMs = a) × b) × c) × d) × e)	**0.000132**

TIM=targeted immune modulator.

Table 2: Unit costs of TIMs	
TIM	**Cost ($)**
adalimumab 40 mg/syringe*	695.17
etanercept 50 mg/syringe†	378.03
infliximab 100 mg/vial*	961.93
alefacept 15 mg/syringe‡	1,249.00
efalizumab 150 mg/vial‡	411.92

*Average of unit costs from Alberta, British Columbia, Saskatchewan, and Québec drug benefit formularies. †Average of unit costs from Alberta, British Columbia, and Québec drug benefit formularies. ‡PPS Pharma; TIM=targeted immune modulator.

Table 3: Annual dosing regimens by TIM		
TIM	**Annual dosing regimen 1st year of treatment**	**Annual dosing regimen subsequent year of treatment**
adalimumab 40 mg/syringe	80 mg SC for 1 week followed by 40 mg SC every 2 weeks (assume 27 injections)	40 mg SC every 2 weeks (assume 26 injections)
etanercept 50 mg/syringe	50 mg SC twice a week for 3 months, then 50 mg SC weekly (assume 64 injections)	50 mg SC weekly (assume 52 injections)
infliximab 100 mg/vial	5 mg/kg IV initial dose, then at weeks 2 and 6, then every 8 weeks after (assume 9 treatments)	5 mg/kg IV every 8 weeks (assume 7 treatments)
alefacept 15 mg/syringe	15 mg IM every week for 12 weeks; may be retreated in 12 weeks (assume 24 injections)	15 mg IM every week for 12 weeks; may be retreated in 12 weeks (assume 24 injections)
efalizumab 150 mg/vial	0.7 mg/kg SC first dose,1 mg/kg SC every week (assume 52 injections)	1 mg/kg SC every week (assume 52 injections)

IM=intramuscular; IV=intravenous; SC=subcutaneous; TIM=targeted immune modulator.

Table 4: Estimates of annual cost of TIM treatment for severe plaque psoriasis					
TIM	**$ In 1st Year of Treatment**	**$ Subsequent Year of Treatment**	**% 1st Year of Treatment**	**Market Share**	**Weighted Annual Cost**
adalimumab 40 mg/syringe	18,769.66	18,074.49	0.04	0.025	$18,102
etanercept 50 mg/syringe	24,194.03	19,657.65	0.04	0.684	$19,839
infliximab 100 mg/vial	38,958.30	30,300.90	0.04	0.190	$30,647
alefacept 15 mg/syringe	29,976.00	29,976.00	0.04	0.025	$29,976
efalizumab 150 mg/vial	21,419.97	21,419.97	0.04	0.076	$21,420
weighted average annual TIM treatment cost					$22,223

TIM=targeted immune modulator.

Table 5: Base case annual treatment costs estimates			
	Population 18+ (000's)	**Number of Adults With Severe Plaque Psoriasis Treated With TIM on Public Drug Plans***	**Total Annual Treatment Costs ($) for Public Drug Plans†**
Canada	25,664.70	1,355	30,105,935
Province or Territory			
Newfoundland and Labrador	411.06	22	482,193
Prince Edward Island	108.36	6	127,115
Nova Scotia	749.23	40	878,881
New Brunswick	601.69	32	705,806
Québec	6,116.83	323	7,175,331
Ontario	9,909.99	523	11,624,890
Manitoba	898.07	47	1,053,478
Saskatchewan	749.16	40	878,802
Alberta	2,595.09	137	3,044,161
British Columbia	3,453.00	182	4,050,535
Yukon Territory	24.20	1	28,395
Northwest Territories	29.65	2	34,790
Nunavut	18.39	1	21,578

*Equals population aged 18+ × 0.0132% × 40%. †Equals number of adults with severe plaque psoriasis treated with a TIM on public drug plans × $22,223. TIM=targeted immune modulator.

Table 6: Sensitivity analysis			
Assumption	**Base Case Value**	**SA Value**	**Total Annual Treatment Costs ($)**
prevalence	1.5%	1.0%	20,070,623
		2.0%	40,141,247
proportion of patients on systemic oral agents who will be treated with a TIM	23.0%	16.0%	20,943,259
		30.0%	39,268,611
proportion of TIM treated patients who have induction therapy	4.0%	0.0%	29,847,247
		10.0%	30,493,967
		50.0%	33,080,848
		75.0%	34,697,648
		100.0%	36,314,448
weight of patient	90 kg	80 kg	29,229,442
		100 kg	30,982,428

SA=sensitivity analyses; TIM=targeted immune modulator.