

Canadian Agency for  
Drugs and Technologies  
in Health



Agence canadienne  
des médicaments et des  
technologies de la santé

## OVERVIEW OF CDR CLINICAL AND PHARMACOECONOMIC REPORTS

**CDR**

March 2008

Adalimumab  
Humira® – Abbott Laboratories Limited  
Indication – Crohn's Disease



*Supporting Informed Decisions*

*À l'appui des décisions éclairées*

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Canadian Agency for  
Drugs and Technologies  
in Health

# COMMON DRUG REVIEW

## Overview of CDR Clinical and Pharmacoeconomic Reports

### Adalimumab

Humira<sup>®</sup> — Abbott Laboratories Ltd.

Indication — Crohn's Disease

March 2008

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## LIST OF ABBREVIATIONS

<b>AE</b>	adverse event
<b>CDAI</b>	Crohn's Disease Activity Index
<b>CI</b>	confidence interval
<b>CR-70/100</b>	clinical response (70 or 100-point CDAI score reduction)
<b>IBDQ</b>	Inflammatory Bowel Disease Questionnaire
<b>mITT</b>	modified intent to treat
<b>NNT</b>	number needed to treat
<b>QALY</b>	quality-adjusted life year
<b>RCT</b>	randomized controlled trial
<b>SAE</b>	serious adverse event
<b>TNF</b>	tumour necrosis factor

## REVIEW IN BRIEF

### Adalimumab (Humira®) — CEDAC Final Recommendation Issued December 19, 2007

*Adalimumab (Humira®) was submitted by the manufacturer to the Common Drug Review (CDR) for consideration for formulary listing by participating public drug plans, for a new indication. This Review in Brief includes the Canadian Expert Drug Advisory Committee's (CEDAC) recommendation and reasons for recommendation, and information used by CEDAC in making its recommendation including: a summary of the best available clinical and pharmacoeconomic evidence identified and reviewed by the CDR, as well as information submitted by the manufacturer.*

### CEDAC Recommendation

CEDAC recommended that adalimumab be listed for moderate to severely active Crohn's disease in patients who are refractory to or who experience contraindications to an adequate course of 5-aminosalicylic acid and corticosteroids and other immunosuppressive therapy. Eligible patients should receive an induction dose of 160 mg followed by 80 mg two weeks later. Clinical response to adalimumab should be assessed four weeks after the first induction dose, using criteria such as a 100-point reduction in the Crohn's Disease Activity Index (CDAI). Ongoing coverage for adalimumab maintenance therapy should only be provided for responders, as noted above, and for a dose not exceeding 40 mg every two weeks.

### Reasons for the Recommendation

- Adalimumab has been demonstrated to be superior at inducing and maintaining remission, compared with standard therapy, and it has been shown to improve measures of quality of life when used during the induction and maintenance phases of therapy.
- Patients who do not respond to the induction phase of treatment with adalimumab appear to derive little benefit from further therapy with adalimumab.
- The annual cost of adalimumab is \$20,700 in the first year and \$18,000 for subsequent years of treatment, which is significantly greater than that for standard therapy (corticosteroids, sulfasalazine, and immunosuppressants), but less than the cost of infliximab (\$29,000 in the first year and \$22,000 thereafter). Infliximab is another anti-

tumour necrosis factor (TNF) agent used for this indication. The manufacturer submitted an economic evaluation, which reported that adalimumab was cost saving when compared with infliximab, and was associated with an incremental cost per quality-adjusted life year (QALY) gained of \$113,000 when compared with standard therapy during a 56-week time horizon. Although the incremental cost per QALY gained is in excess of traditional standards, infliximab is currently funded by most public drugs plans for use in Crohn's disease.

- Given that there are no randomized controlled trials (RCTs) that evaluate the impact of increasing the maintenance dose of adalimumab beyond 40 mg every two weeks, and there are significant safety concerns associated with the use of all anti-TNF agents, CEDAC was not supportive of escalating doses beyond 40 mg every two weeks.

### Drug

- Adalimumab is approved by Health Canada for reducing signs and symptoms, and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who had an inadequate response to conventional therapy.
- It is also indicated for reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.
- Adalimumab, an anti-TNF biologic agent, is a recombinant, human monoclonal antibody that binds to TNF alpha.
- The recommended induction dose regimen for adult patients with Crohn's disease is 160 mg at week 0, followed by 80 mg at week 2. The recommended maintenance dose regimen for adult patients with Crohn's disease is 40 mg every other week beginning at week 4.

### Condition

Crohn's disease is a chronic inflammatory disease that can affect any portion of the gastrointestinal tract, from the mouth to the perianal area. It is characterized by transmural inflammation and has the potential to include systemic and extraintestinal complications.

## Clinical Review

- A systematic review of double-blind RCTs of adalimumab in patients with moderate to severely active Crohn's disease was undertaken.
- Four placebo-controlled RCTs met the inclusion criteria for the systematic review.
- Two trials were induction trials of four-week duration with a total of 624 patients, and two trials were one-year maintenance trials.
- One induction trial and one maintenance trial included patients who had lost response or were intolerant to infliximab.

## Results

### Induction Trials (two trials)

Adalimumab was associated with statistically significant improvements in:

- quality of life
- rates of remission [number needed to treat (NNT)=4 to 7].

### Maintenance Trials (two trials)

One trial treated all patients with open-label adalimumab for four weeks, after which 499 patients who responded and 279 patients who did not respond were randomized to maintenance therapy with adalimumab or placebo.

In the non-responders there was:

- no difference in remission between those treated with adalimumab or placebo after one year.

In the responders:

- adalimumab resulted in statistically significant improvements in:
  - quality of life
  - remission rates (NNT=4)
  - rate of corticosteroid discontinuation (NNT=4)

In a second trial, 55 patients were randomized to adalimumab or placebo. After 56 weeks there were no statistically significant differences in:

- quality of life
- remission rates (based on manufacturer's unpublished data)
- rates of corticosteroid discontinuation.

## Adverse Events

- All patients were exposed to adalimumab in the maintenance trials, making it difficult to draw conclusions about potential harms.
- The product monograph highlights the potential for serious adverse events, including infections and malignancies.

## Pharmacoeconomic Review

The pharmacoeconomic analysis submitted by the manufacturer was assessed and critiqued.

## Highlights

- The annual cost of adalimumab is \$20,700 in the first year and \$18,000 for subsequent years of treatment, which is less than the cost of infliximab at \$29,000 in the first year and \$22,000 thereafter. The annual cost of medications associated with standard care (<\$1,700) is less than that of adalimumab.
- Within the manufacturer's economic evaluation, one analysis compared adalimumab with standard care, during a 56-week time horizon, in which an incremental cost per QALY of \$113,000 was reported. Based on the CDR re-analysis, there is potential for the cost per QALY to be higher; however, adalimumab may lead to longer-term benefits not captured in the 56-week timeframe.
- In a second analysis, the manufacturer compared adalimumab with infliximab in patients who were naïve to anti-TNF treatments. This evaluation reported that adalimumab is less expensive, and more patients experienced remission with it. While adalimumab may be less costly than infliximab, it is unclear whether an efficacy advantage exists.

### What is the CDR?

The CDR conducts objective, rigorous reviews of the clinical and cost-effectiveness of drugs, and provides formulary listing recommendations to the publicly funded drug plans in Canada (except Québec).

## OVERVIEW

### Context

This document is an overview of two Common Drug Review (CDR) reports: the CDR Clinical Review Report (a systematic review of the clinical evidence) and the CDR Pharmacoeconomic Review Report (a critique of the pharmacoeconomic evaluation submitted by the manufacturer). These reports were prepared by the CDR to support the Canadian Expert Drug Advisory Committee (CEDAC) in making a formulary listing recommendation to participating publicly funded drug plans. The reviews are an assessment of the best available evidence that the CDR has identified and compiled, including that submitted by the manufacturer.

This overview is based on the adalimumab CDR Clinical Review Report, 61 pages in length with 84 references, and the adalimumab CDR Pharmacoeconomic Review Report, 23 pages with eight references. The manufacturer had the opportunity to provide feedback on each of the full reports and on this Overview Report. The CDR has considered the feedback in preparing the final versions of all of these reports. The manufacturer's confidential information as defined in the [CDR Confidentiality Guidelines](#), may have been used in the preparation of these documents and thus considered by CEDAC in making its recommendation. The manufacturer has reviewed this document and has not requested the deletion of any confidential information.

### Introduction

Crohn's disease is a chronic inflammatory disease that can affect any portion of the gastrointestinal tract, from the mouth to the perianal area. It is characterized by transmural inflammation and has the potential to include systemic and extraintestinal complications. It may be defined by location (e.g., terminal ileal, colonic, ileocolic, or upper gastrointestinal) or by pattern of disease (e.g., inflammatory, perforating, or stricturing).<sup>1</sup> Although it can affect any age group, the peak onset of disease is most often seen in the second or third decade. Crohn's disease is a chronic, incurable, relapsing condition. A patient is considered to be in clinical remission when there are few or no symptoms. A relapse or disease flare can be defined as the recurrence of symptoms in a patient with established Crohn's disease who was previously in clinical remission.

There are two goals in providing therapy for Crohn's disease: induce remission and maintain remission. Treatment choices are based on the site and extent of the disease, and on the severity of symptoms. Current first-line therapy consists of aminosalicylates, antibiotics, or corticosteroids (budesonide); second-line therapy consists of corticosteroids (prednisone); third-line therapy consists of immunosuppressants (azathioprine, 6-mercaptopurine, or methotrexate); and anti-tumour necrosis factor (TNF) biologic agents (infliximab or adalimumab) for patients who have failed all other treatment options.<sup>2</sup>

Adalimumab, an anti-TNF biologic agent, is a recombinant monoclonal antibody that binds to human TNF alpha. It is indicated for reducing signs and symptoms, and inducing and maintaining clinical remission in adult patients with moderate to severe Crohn's disease who had an inadequate response to conventional therapy, including corticosteroids and/or immunosuppressants. It is also indicated for reducing signs and symptoms, and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab, another anti-TNF biologic agent.

Adalimumab is supplied in a pre-filled syringe, or a pre-filled pen device. The recommended induction dose regimen for adult patients with Crohn's disease is 160 mg at week 0 (dose can be administered as four injections in one day or as two injections per day for two consecutive days), followed by 80 mg at week 2. The recommended maintenance dose regimen for adult patients with Crohn's disease is 40 mg every other week beginning at week 4. For patients who experience a disease flare, dose escalation may be considered. The product monograph does not specify a maximum dose, but it states that some patients who experience a decrease in their response may benefit from an increase in dose to 40 mg every week.

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## Clinical Review

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### **Objective**

To evaluate the impact of adalimumab on patient outcomes compared with appropriate comparators and placebo in the treatment of patients with Crohn's disease who had an inadequate response to conventional therapy (including corticosteroids, immunosuppressants, and/or infliximab).

### **Methods**

For information about the methodology employed in the full CDR Clinical Review of adalimumab, refer to Appendix I.

### **Selection Criteria**

Studies were chosen for inclusion in the review based on the criteria listed in Table 1.

# Common Drug Review

**Table 1: Selection Criteria**

Clinical Trial Design	Patient Population	Interventions	Appropriate Comparators*	Outcomes (measured by validated methods)
Unpublished or published DB RCTs	<p>Patients with moderate to severe Crohn's disease.</p> <p>Subgroup analyses performed where possible based on Crohn's disease severity at baseline and on patients refractory of and/or intolerance to infliximab.</p>	Adalimumab as monotherapy or in combination with other medications, at doses up to the recommended dose.	<p>Infliximab</p> <p>Azathioprine</p> <p>6-mercaptopurine</p> <p>Methotrexate</p> <p>Corticosteroids</p> <p>Placebo</p>	<ul style="list-style-type: none"> <li>• Remission rate</li> <li>• Time to remission and time to loss of remission</li> <li>• Quality of life</li> <li>• Return to work</li> <li>• Crohn's disease symptom improvement and response rate</li> <li>• Incidence of strictures, fistulas surgery for Crohn's disease, bowel obstruction.</li> <li>• SAEs; mortality</li> <li>• Steroid discontinuation</li> <li>• Hospitalization (all-cause and Crohn's disease symptom related)</li> <li>• Withdrawals and WDAEs</li> <li>• C-reactive protein levels</li> <li>• Antibody development to adalimumab</li> <li>• AEs</li> </ul>

AEs=adverse events; DB=double blind; RCT=randomized controlled trial; SAEs=serious adverse events; WDAEs=withdrawals due to adverse events.

\*Standard therapies available in Canada (may include drug or non-drug interventions)

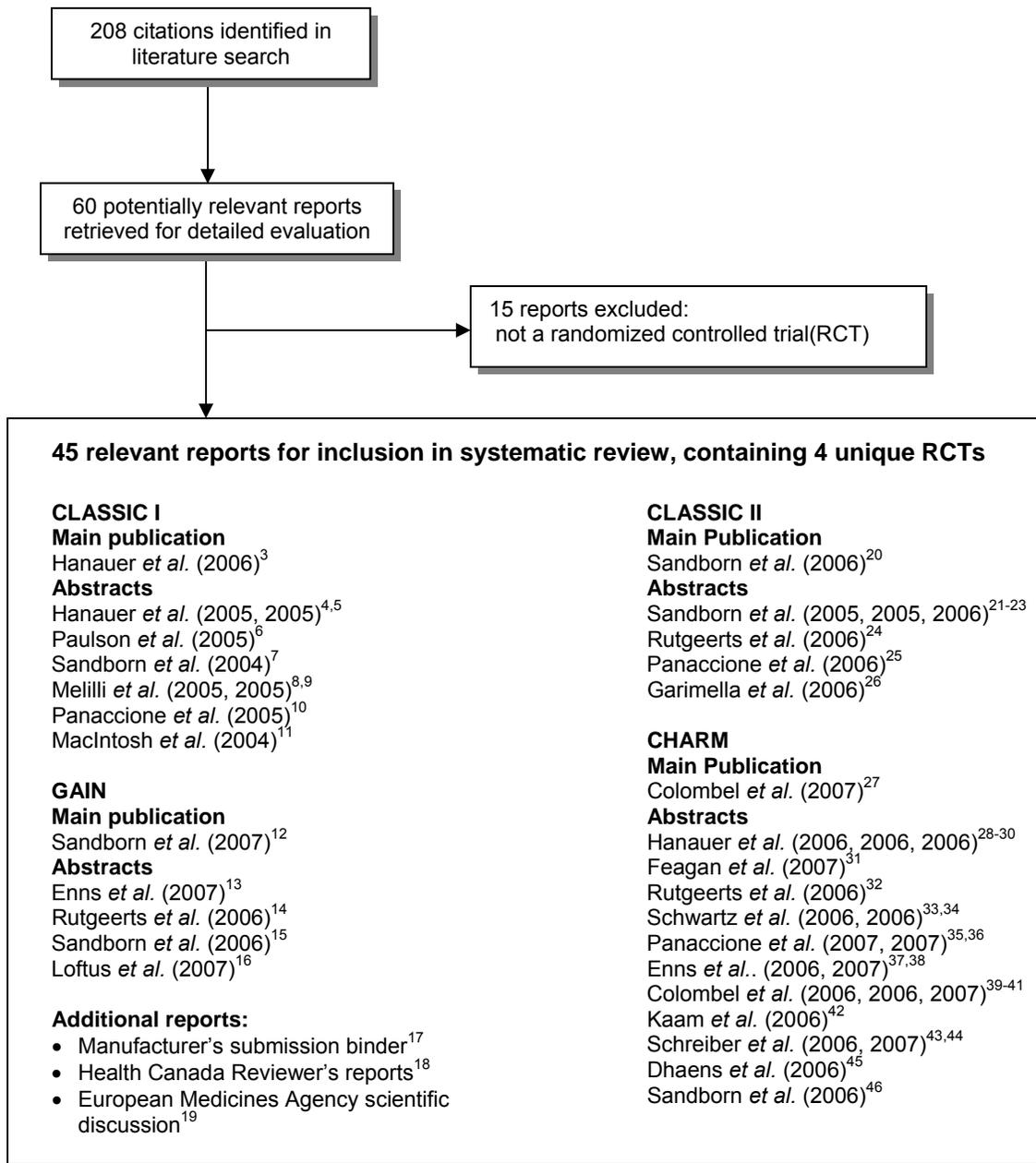
Note: The following definitions will be used based on the Crohn's Disease Activity Index (CDAI).

Remission: CDAI <150; mild Crohn's disease: CDAI 150-220; moderate Crohn's disease: CDAI 221-300; severe Crohn's disease: CDAI 301-450; very severe Crohn's disease: CDAI >450.

## Results

### Findings from the Literature

Figure 1: QUOROM Flowchart Detailing Flow of Studies



## Summary of Evidence

### *Included Studies and Trial Characteristics*

Four double-blind RCTs in patients with moderate to severe Crohn's disease met the inclusion criteria for this CDR report.<sup>3,12,20,27</sup> All trials were placebo-controlled. Two were four-week induction trials (CLASSIC I: N=299, GAIN: N=325) and two were one-year maintenance trials (CLASSIC II: N=55; CHARM randomized responder population: N=499, randomized non-responder population: N=279). CLASSIC II was an extension trial to CLASSIC I and most patients from CLASSIC I entered the CLASSIC II trial, but not all were randomized. In the CLASSIC II trial (Appendix II for the study schematic), there was a four-week open-label run-in period, in which patients received adalimumab 40 mg every other week. Subjects who were in remission at weeks 0 and 4 of CLASSIC II were randomized again (N=55). In the CHARM trial (Appendix II for the study schematic), responders and non-responders were randomized after a four-week open-label induction period, but the manufacturer's primary analysis was performed in randomized responders (N=499).

The GAIN and CHARM trials enrolled patients who had lost response or who had intolerance to infliximab. The CHARM trial also enrolled anti-TNF naïve patients. The other trials exclusively enrolled anti-TNF naïve patients. Concomitant use of corticosteroids, immunosuppressants, and other agents to treat Crohn's disease were permitted during the trials at stable doses.

## Summary of Results

See Table 2 for a summary of trial outcomes.

### *Efficacy*

Results stated below compare approved adalimumab doses only; adalimumab 160 mg at week 0 plus adalimumab 80 mg at the week 2 regimen versus placebo for induction trials, or adalimumab 40 mg at the every other week regimen versus placebo for maintenance trials.

### *Induction Trials*

- The proportion of patients with remission (CDAI<150) at week 4 was statistically significantly higher in the adalimumab group versus placebo for CLASSIC I [number needed to treat (NNT) (95% confidence interval (CI)): 4(3, 9)] and GAIN trials [NNT (95% CI): 7(5,15)].
- Results for both induction trials demonstrated a statistically significant improvement in quality of life, as measured by the Inflammatory Bowel Disease Questionnaire (IBDQ) at week 4 for adalimumab compared with placebo. The mean difference was approximately 14 points on a 224-point scale. For further information on the IBDQ refer to Appendix III.

### *Maintenance Trials*

- The CLASSIC II results did not demonstrate any statistically significant improvements for adalimumab 40 mg every other week compared with placebo for outcomes of remission, quality of life, corticosteroid discontinuation, or CR-70/CR-100 response (a decrease from baseline of  $\geq 70$  or  $\geq 100$  points in CDAI). (Note: the information regarding remission is from the manufacturer's unpublished documents and differs from published data regarding the CLASSIC II trial.)
- In the CHARM trial, the randomized responder population was comprised of subjects who achieved a CR-70 response at week 4 after open-label induction therapy with adalimumab. In the randomized responder population, adalimumab patients achieved higher remission

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rates than placebo and this was statistically significant at week 56 [NNT (95% CI): 4(3, 6)]. In the randomized non-responder population (i.e. those who did not achieve CR-70 during induction phase), there was no statistically significant difference in remission rate between adalimumab and placebo subjects, except at week 26.

- The CHARM trial results demonstrated a statistically significant improvement in quality of life, as measured by the IBDQ score at week 56 for adalimumab compared with placebo [mean difference of change (95% CI): 14.4(4.2, 24.5)]. But there was no difference in SF-36 (the short-form health survey) Physical Component Summary results between adalimumab and placebo at 56 weeks.
- In the CHARM trial, the rate of corticosteroid discontinuation in adalimumab patients was 29% (17 of 58) versus 5% (three of 66) in placebo subjects at week 56 [NNT(95% CI): 4(3,9)], as reported in the manufacturer's unpublished data.

## *Harms*

- The rates of overall serious adverse events (SAEs), infectious SAEs, and overall adverse events (AEs) were similar between the adalimumab and placebo groups in the induction studies. The number of subjects with SAEs was lower in the maintenance trials in the adalimumab groups compared with placebo. In the maintenance trials, the number of infectious AEs was slightly higher in subjects taking adalimumab 40 mg every other week compared with placebo.

**Table 2: Summary of Trial Outcomes**

Trial Design and Baseline Characteristics						Results			
Trial	Design	Adalimumab Doses, Week 0/2	Baseline CDAI>300, n (%) Population	Prior IFX	Concomitant Baseline CD Drugs, n(%)	CDAI<150 RR (95% CI) NNT (95% CI)	CR-100 RR (95% CI) NNT (95% CI)	IBDQ* MDC(95% CI)	CS d/c RR (95% CI) NNT (95% CI)
<b>CLASSIC I (induction) N=299</b>	DB RCT 4 weeks	40 mg/20 mg or 80 mg/40 mg or 160 mg/80 mg	119(40)  Moderate to severe CD	Anti-TNF naïve	CS: 93(31) IS: 88(29) CS+IS: 32(11)	Week 4 2.9 (1.5, 5.8) 4 (3,9)	Week 4 2.1 (1.3, 3.4) 4 (2,8)	Week 4 13.1 (3.5, 22.7)	NR
<b>GAIN (induction) N=325</b>	DB RCT 4 weeks	160 mg/80 mg	169(52)  Moderate to severe CD	Anti-TNF experienced	CS: 128(39) IS: 158(49) CS+IS: 71(22)	Week 4 3.0 (1.6, 5.5) 7 (5, 15)	Week 4 1.6 (1.1, 2.2) 7 (4, 26)	Week 4 14.2 (7.9, 20.4)	NR
<b>CLASSIC II (maintenance) N=55</b>	DB RCT 56 weeks	40 mg qw or 40 mg qow	NR  Randomized remitters	Anti-TNF naïve	CS: 25(46) IS: 12(22) CS+IS: 5(9)	Week 56 1.4 (0.6, 3.2) NSS	Week 56 1.4 (0.6, 3.2) NSS	Week 56 NSS	NC
<b>CHARM (maintenance) RRP N=499</b>	4 week OL induction, +52-week DB RCT	80 mg/40 mg  40 mg qw or 40 mg qow	268(54)  Randomized responders	48% anti-TNF experienced	CS: 198(40) IS: 239(48) CS+IS: NR	Week 56 3.1 (1.9, 4.8) 4 (3,6)	Week 56 2.5 (1.7, 3.7) 4 (3,6)	Week 56 14.4(4.2, 24.5)	Week 56 6.5 (2.0, 20.1) 4 (3,9)

CD=Crohn's disease; CDAI=Crohn's Disease Activity Index; CR-100= clinical response (100 point CDAI score reduction); CS=corticosteroids; DB=double blind; d/c=discontinuation; IBDQ=Inflammatory Bowel Disease Questionnaire; IFX=infliximab; IS=immunosuppressants; MDC=mean difference of change from baseline; mITT=modified intent to treat (randomized responder population); NC=not calculated by CDR (numbers too small to calculate meaningful statistic); NNT=number needed to treat; NR=not reported; NSS=not statistically significant; OL=open label; qow=every other week; qw=every week; RCT=randomized controlled trial; RR=relative risk; RRP=randomized responder population; TNF=tumour necrosis factor.  
\* Positive changes in IBDQ score favour adalimumab.

**Notes**

- Table 2 includes both published and unpublished data.
- Statistics by CDR. RR values above one and positive IBDQ values favour adalimumab.
- All results compare approved adalimumab doses only; adalimumab 160 mg week 0 plus adalimumab 80 mg week 4 regimen versus placebo for induction trials, or adalimumab 40 mg every other week regimen versus placebo for maintenance trials.  
Subjects in the GAIN and CHARM trials had more severe disease at baseline than those in CLASSIC I/II, as indicated by the higher percentages of subjects with baseline CDAI >300.

## Discussion

The trials in the CDR systematic review of adalimumab included two induction trials and two maintenance trials. The high discontinuation rate in some trials increased the risk of bias. Attrition was low in the shorter induction trials, but in the maintenance trials there was a significant proportion of randomized subjects who did not complete the trials, or who completed the trial but only after they had switched to open-label adalimumab. This obscures the quantification of relative efficacy and harms. The statistical analysis used in the maintenance trials counted patients as remission failures if they switched to open-label adalimumab or discontinued the study altogether. This may reduce the chance of bias that is reflected in the results, but this risk of bias does remain due to high attrition from the double-blind treatment.

The characteristics of patients enrolled in the trials were generally reflective of individuals who might be prescribed adalimumab in Canada and for whom reimbursement is being sought. The doses used in the four trials were not always reflective of the recommended doses, but the results in the CDR review focused on the recommended doses. Generalizability of the CHARM trial is hampered by the fact that subjects received induction doses (80 mg/40 mg) that are lower than those recommended in the Canadian product monograph.

The CLASSIC II trial was designed to study if remission is maintained over time, but did not demonstrate statistically significant differences in remission, possibly due to the small sample size of the randomized cohort. The low doses used in the CLASSIC I trial contributed to the low number of subjects eligible for CLASSIC II since only those who were in remission were eligible for CLASSIC II.

The CHARM trial provided the most robust data available on the use of adalimumab in both anti-TNF naïve and experienced subjects. The length of follow-up is limited to one year in the CHARM trial, and data on remission during a longer period of time were not available to CDR at the time of the CDR review. This is an important limitation, given the chronic nature of Crohn's disease.

### *Efficacy*

#### Induction Trials:

- It appears that CLASSIC I patients, who had less severe Crohn's disease at baseline, responded slightly better to the induction regimen of adalimumab than did the more severe Crohn's subjects in GAIN.
- A post-hoc subgroup analysis in the induction trials indicated that adalimumab may result in higher remission rates in patients also taking corticosteroids for induction compared with those not taking corticosteroids. This is an interesting finding, but should be interpreted cautiously since the analysis was performed post-hoc. There was no other statistical evidence of effect modification for the other factors, including previous anti-TNF use and baseline CDAI score.

#### Maintenance Trials:

- The NNT of four, for remission at week 56 in the CHARM trial, supports the efficacy of adalimumab. There were improvements in quality of life, as measured by mean IBDQ scores; however, the clinical significance of a 14-point improvement is uncertain and the SF-36 results did not show any improvement. Other outcomes of response, time to loss of remission, and corticosteroid discontinuation (NNT of four) were statistically significant in favour of adalimumab compared with placebo.

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- The remission results in the randomized non-responder population suggest that there is little benefit in continuing adalimumab therapy in patients without an early response. The adalimumab product monograph allows for the possibility of continuing adalimumab therapy for 12 weeks in patients who do not respond by week 4, but the CHARM randomized data do not provide support for this practice if remission (CDAI <150) is the goal of therapy.
- The CHARM pre-specified subgroup analysis that examined remission rates by previous anti-TNF status showed a numerically higher response rate in patients who were anti-TNF naïve (adalimumab 40 mg every other week: 42%; placebo: 14%), compared with those who had taken anti-TNF agents (adalimumab 40 mg every other week: 30%; placebo: 10%), but the test for interaction was not statistically significant.

## *Harms*

- The number of subjects with SAEs was lower in the adalimumab groups compared with placebo in the maintenance trials and this was statistically significant. Harms data from controlled trials beyond one year were lacking for patients with Crohn's disease at the time of the CDR review.
- The rate of formation of antibodies to adalimumab in all trials was low. The highest incidence was seen in the open-label arm of the CLASSIC II trial (six of 215 or 2.8%). There were no analyses provided that assessed the impact of immunogenicity formation on the efficacy of adalimumab.
- The adalimumab product monograph highlights several important serious warnings and precautions. These include: opportunistic infections, nervous system disease, malignancies, and lupus-like symptoms. The risk of serious infections is well established with TNF blockers, including adalimumab, with the most notable infectious complication being the reactivation of tuberculosis and hepatitis B.

## *Other Considerations*

- Evidence of the effect of dose escalation comes from the CHARM trial and is based on patients who were unblinded and switched to open-label adalimumab. While the data provided some insight into the effect of dose escalation, it is entirely based on open-label uncontrolled treatment. Therefore, dose escalation due to inadequate response or flare cannot be supported because of the limitations of these data.
- None of the trials compared adalimumab with infliximab. This is a notable omission because infliximab is indicated for use in patients who have failed conventional treatment and is often recommended as the last stage in stepped therapy guidelines. A similar use for adalimumab is possible. The mode of administration of adalimumab (subcutaneous) may represent a convenience advantage compared with infliximab (intravenous infusion).

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## Pharmacoeconomic Review

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### **Context**

The CDR assesses and critiques the economic evaluation, submitted by the manufacturer, with respect to its quality and validity, including the appropriateness of the methods, assumptions and inputs, and results. The CDR may provide additional information on the cost-effectiveness of the submitted drug, where relevant, from other sources or by using the economic model to consider other scenarios.

### **Objective of the Manufacturer's Submitted Economic Evaluation**

Is adalimumab a cost-effective strategy in the treatment of adult patients with moderately to severely active Crohn's disease who have not responded adequately to other treatment options, under the publicly funded health care system in Canada versus:

- standard care (conventional non-anti-TNF treatment)?
- infliximab 5 mg/kg maintenance treatment?

### **Summary of the Manufacturer's Pharmacoeconomic Submission**

The manufacturer submitted two economic models in support of the cost-effectiveness of adalimumab for the treatment of patients with moderate to severely active Crohn's disease (defined as CDAI  $\geq 150$ ) over a 56-week time horizon. The first model considered the comparison of adalimumab with standard care (e.g., corticosteroids, sulfasalazine). Using this model, the manufacturer further considered the treatment of a severe population (CDAI  $\geq 300$ ) over the time horizon of a lifetime. This model was based on four Crohn's disease health states (remission, moderate, severe, and very severe), defined by CDAI scores. Data on the clinical effectiveness of adalimumab were obtained from the CHARM trial,<sup>27</sup> while clinical effectiveness of standard care was derived from the placebo arm of the four-week CLASSIC I induction trial.<sup>3</sup> Quality of life and cost information were obtained from various sources, including literature,<sup>12,47</sup> a survey of Crohn's specialists in Canada,<sup>47</sup> and cost information from the Ontario Schedule of Benefits (April 2007) and the Ontario Case Costing Initiative (2004-2005). The second economic model considered the comparison of adalimumab with infliximab. Given the lack of a comparative study, the authors used a weighting method to simulate a cohort of patients from the CHARM trial that matched the baseline age, gender, and CDAI score of patients from the infliximab trial, ACCENT I.<sup>48</sup> The analysis considered the treatment of anti-TNF naïve patients only. The cost of treatment, administration, wastage associated with infliximab, and hospitalizations were also considered.

### **Cost Comparison**

CDR produced Table 3 to provide a comparison of the cost of treatment of the submitted drug with comparator treatments deemed appropriate by clinical experts. Comparators may reflect recommended or actual practice. Comparators are not restricted to drugs, but may include devices or procedures where appropriate. Costs are manufacturer list prices, unless otherwise specified.

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**Table 3: Cost Comparison of Adalimumab versus Comparator Treatments**

Drug / Comparator	Strength	Dosage Form	Price	Recommended Use <sup>†</sup>	Average Daily Drug Cost	Average Annual Cost
Adalimumab (Humira)*	40 mg syringe	Pre-filled syringe	\$691.3500	At week 1: 160 mg At week 2: 80 mg At week 4: 40 mg sc every other week thereafter	Yr 1: \$57  Yr 2 and on: \$49	Yr 1: \$20,739  Yr 2: \$17,975
Infliximab (Remicade)	100 mg/vial	Injection	\$940.0000	5 mg/kg IV at weeks 0, 2 and 6 then every 2 months thereafter <sup>‡</sup>	Yr 1: \$82  Yr 2 and on: \$62	Yr 1: \$29,930  Yr 2: \$22,360
Prednisone	5 mg 50 mg	Tablet	\$0.0220 \$0.0913	40 -60 mg daily for 2 -3 weeks to induce remission, taper to 5 -10 mg daily	\$0.18-0.26  \$0.02-0.04	\$66-\$95  \$7-\$15
Sulfasalazine (Salazopyrin and generics)	500 mg 500 mg	Tablet Ent tablet	\$0.1804 \$0.2816	1 -2 g twice to four times daily	\$0.72-4.51	\$263-\$1,646
Olsalazine (Dipentum)	250 mg	Capsule	\$0.4961	500 mg twice to four times daily	\$1.98-3.97	\$723-\$1,449
Budesonide (Entocort)	3 mg	Capsule	\$1.5240**	6 - 9 mg daily	\$3.04-4.60	\$1,110-\$1,679
<b>Drugs Used Off-Label</b>						
Cyclosporine (Neoral)	25 mg 50 mg 100 mg	Capsule	\$0.9952 \$1.9400 \$3.8815	5 - 7.5 mg/kg daily divided every 12 hours <sup>#</sup>	\$13.58- \$20.37	\$4,957-\$7,435
Methotrexate	50 mg/2 mL 20 mg/2 mL	Injection injection	\$12.4800 \$12.5000	25 mg IM/SC weekly for 16 to 24 weeks to induce remission, then 15 mg weekly IM/SC	\$0.89  \$0.53	\$234-\$254 <sup>§</sup>  \$194 <sup>Δ</sup>
Azathioprine (Imuran and generics)	50 mg	Tablet	\$0.4300	2 - 3.5 mg/kg daily <sup>#</sup>	\$1.29-2.15	\$471-\$785
6-mercaptopurine (Purinethol)	50 mg	Tablet	\$3.6680	1 - 2.5 mg/kg daily <sup>#</sup>	\$5.50-12.84	\$2,008-\$4,687

Ent=enteric coated; SC=subcutaneously; IM=intramuscular; IV=intravenous; Yr=year.

Source: Ontario Drug Benefit Program (ODB) (2007).

\*Manufacturer's submission binder. The price per syringe is \$691.35 per syringe, except in British Columbia (\$686.59) and Ontario (\$679.80).

<sup>†</sup>As reported in ODB utilization (2004/2005), unless otherwise indicated.

<sup>‡</sup>Based on 70 kg patient; wastage may occur.

\*\*Alberta Formulary (2007).

<sup>#</sup>Based on 70 kg patient.

<sup>§</sup>Based on induction and maintenance doses for one year.

<sup>Δ</sup>Based on maintenance dose for one year.

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## Results (as submitted by the manufacturer)

- Compared with infliximab, adalimumab costs less and provides more QALYs during a one-year time period. Adalimumab is dominant (Table 4).
- Compared with standard care, adalimumab was associated with a one-year incremental cost per QALY of \$112,991 (Table 5).

**Table 4: Adalimumab Compared with Infliximab in Base-Case Analysis (56 weeks)**

Cost Type	Adalimumab	Infliximab	Difference
Anti-TNF treatment costs	\$20,063	\$23,726	(\$3,663)
Administration costs	\$0	\$600	(\$600)
Overdose drug costs	\$0	\$3,149	(\$3,149)
Drug costs	\$20,063	\$27,475	(\$7,411)
Hospitalization costs	\$1,948	\$2,989	(\$1,042)
Disease state costs	\$773	\$860	(\$87)
<b>TOTAL cost</b>	<b>\$22,784</b>	<b>\$31,324</b>	<b>(\$8,540)</b>

Source: Pharmacoeconomic Evaluation in Manufacturer's submission binder.

**Table 5: Adalimumab Compared with Standard Care in Base-Case Analysis (56 weeks)**

Cost Type	Adalimumab	Standard Care	Difference
Anti-TNF drug costs	\$15,756	\$0	\$15,756
Disease state costs	\$630	\$1,141	(\$511)
Hospitalization costs	\$2,429	\$7,467	(\$5,038)
Total direct costs	\$18,815	\$8,608	\$10,207
<b>EFFECTS</b>			
QALYs	0.8647	0.7743	0.0903
<b>COST per QALY</b>			<b>\$113,034*</b>

TNF=tumour necrosis factor; QALY=quality-adjusted life year.

Source: Pharmacoeconomic Evaluation in Manufacturer's submission binder.

\*The manufacturer calculates a cost per QALY figure of \$112,991. (Differences in the numbers are due to rounding.)

## Pharmacoeconomic Analysis Discussion Points

In reviewing the manufacturer's submission, the reviewers noted the following:

- *Imputation of missing clinical data.* A significant difference in the incremental cost per QALY was observed when using different imputation methods for the clinical data. The manufacturer considers "last value carried forward" in their base case. In their sensitivity analysis, they considered the placebo method, which assumes patients with missing data acquire benefits as if they were on standard care therapy, leading to slightly elevated hospitalization and disease state costs. When using the placebo method approach, the incremental cost per QALY estimate comparing adalimumab with standard care increases to \$163,000 from the base-case estimate of \$113,000.
- *Patient population.* The manufacturer indicates that their base-case analysis is conducted in patients with moderate to severe disease (CDAI  $\geq 150$ ). It should be noted that clinical trials on which the analysis are based only considered patients with baseline CDAI scores  $\geq 220$ , consequently these results may not apply to patients with baseline CDAI scores between 150 and 219.

- *Subgroup analysis for CDAI  $\geq 300$ .* The manufacturer's base-case analysis includes patients with moderate to severe disease (CDAI  $\geq 150$ ) and patients with severe disease (CDAI  $\geq 300$ ). The CDR clinical reviewers note that there is a lack of a statistically significant difference in remission rates between patients with moderate (CDAI=220 to 300) and severe disease (CDAI  $>300$ ), as observed in the induction trials and CHARM (not reported in CLASSIC II). As a result, the benefit modelled by the manufacturer and the lower cost-effectiveness ratio reported for patients with severe disease does not appear to be supported by the clinical trial evidence. However, it should be noted that the clinical trials were not powered to detect differences between moderate and severe disease patient groups.
- *Utility estimates.* The manufacturer has linked utility values to CDAI scores. Because the utility estimate for very severe disease is based on the responses of six people, the 95% CI around the estimate for very severe disease (0.433) is wide (0.027 to 0.83). When considering a higher utility value for very severe disease (0.59), based on the average decrease in utility, the cost per QALY increases to \$137,000 compared with standard care.

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## Summary of the Clinical and Pharmacoeconomic Reviews

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- In anti-TNF naïve and experienced patients:
  - adalimumab is more effective than placebo in inducing remission (CDAI $<150$ ) (NNT of four to seven for remission at week 4).
  - adalimumab treatment resulted in modest improvements in quality of life during the four-week induction period, compared with placebo.
- In patients who have an early response:
  - adalimumab is more effective than placebo at inducing and maintaining remission in patients (NNT of four for remission at week 56).
  - a higher rate of corticosteroid discontinuation and variable changes in quality of life were observed, compared with placebo.
- The overall incidence of SAEs was lower in patients taking adalimumab compared with placebo in a one-year trial. The ability to identify differences in specific SAEs was limited due to the length of the trials and the rarity of some events previously associated with adalimumab use.
- The annual cost of adalimumab is \$20,700 in the first year and \$18,000 for subsequent years of treatment. This is less than the cost of infliximab at \$29,000 in the first year and \$22,000 thereafter. The annual cost of medications associated with standard care (e.g., corticosteroids, sulfasalazine) is less than that of adalimumab ( $< \$1,700$ ).
- In comparison with standard care, the incremental cost per QALY of adalimumab was reported by the manufacturer to be \$113,000. Based on the CDR re-analysis, there is potential for the cost per QALY to be higher; however, adalimumab may lead to longer-term benefits not captured in the analysis.
- In an indirect comparison with infliximab provided by the manufacturer, adalimumab was found to be less expensive, with more patients experiencing remission. While, adalimumab may be less costly (given that its administration is less costly), it is unclear whether an efficacy advantage exists.

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## **CEDAC Final Recommendation — Issued December 19, 2007**

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Following careful consideration and deliberation of the information contained within the CDR Clinical and Pharmacoeconomic Review Reports, CEDAC recommended that adalimumab be listed for moderate to severely active Crohn's disease in patients refractory to or with contraindications to an adequate course of 5-aminosalicylic acid and corticosteroids, and other immunosuppressive therapy. Eligible patients should receive an induction dose of 160 mg followed by 80 mg two weeks later. Patients who respond to the induction dose should receive adalimumab at a dose not exceeding 40 mg every two weeks. Response is defined by criteria such as a 100-point reduction in the Crohn's Disease Activity Index (CDAI).

## APPENDIX I: METHODOLOGY FOR THE FULL CDR CLINICAL REVIEW

### Methods

#### Reviewer Information

- The systematic review of clinical trials was prepared by two CDR clinical reviewers in consultation with an external clinical expert specializing in gastroenterology.
- The supplemental issues were prepared by two clinical reviewers.
- Background information on the condition was prepared by a clinical reviewer in conjunction with an external clinical expert specializing in gastroenterology.

#### Systematic Review Methods

##### Review Protocol

- The review protocol was developed jointly by the two CDR clinical reviewers and the external clinical expert in consultation with the internal and external pharmacoeconomic reviewers. Members of CEDAC also provided input and comments.

##### Literature Search Methods

- The literature search was performed by a CDR information specialist using a peer-reviewed search strategy.
- Published literature was identified by searching the following bibliographic databases: BIOSIS Previews, EMBASE and Medline through OVID, and The Cochrane Library (2007, Issue 3) through Wiley InterScience.
- Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. The initial search was completed on August 3, 2007. Regular alerts were established to update the search until CEDAC's November 21, 2007 meeting.
- Grey literature was obtained by searching the web sites of regulatory, health technology assessment and near-technology assessment agencies, and clinical trial registries. Google and other online search engines were used to search for a variety of web-based information, including conference abstracts.
- In addition, the manufacturer of the drug was contacted for information regarding additional trial data.

##### Selection of Studies

- Each CDR clinical reviewer independently selected studies for inclusion according to the predetermined selection criteria. All articles that were considered potentially relevant by at least one reviewer were acquired from library sources. Reviewers independently made the final selection of studies to be included in the review and differences were resolved through discussion.

## **Selection Criteria**

- Studies were chosen for inclusion in the review based on the criteria listed in Table 1, located in the body of this report.

## **Quality Assessment**

- Study bias was critically assessed independently by the two CDR clinical reviewers.

## **Data Analysis Methods**

- Data were extracted from published literature and unpublished literature provided by the manufacturer. CDR clinical reviewers calculated relative risks (RRs), 95% confidence intervals (CIs), and numbers needed to treat (NNT) where appropriate.

## **Methods for Supplemental Issues**

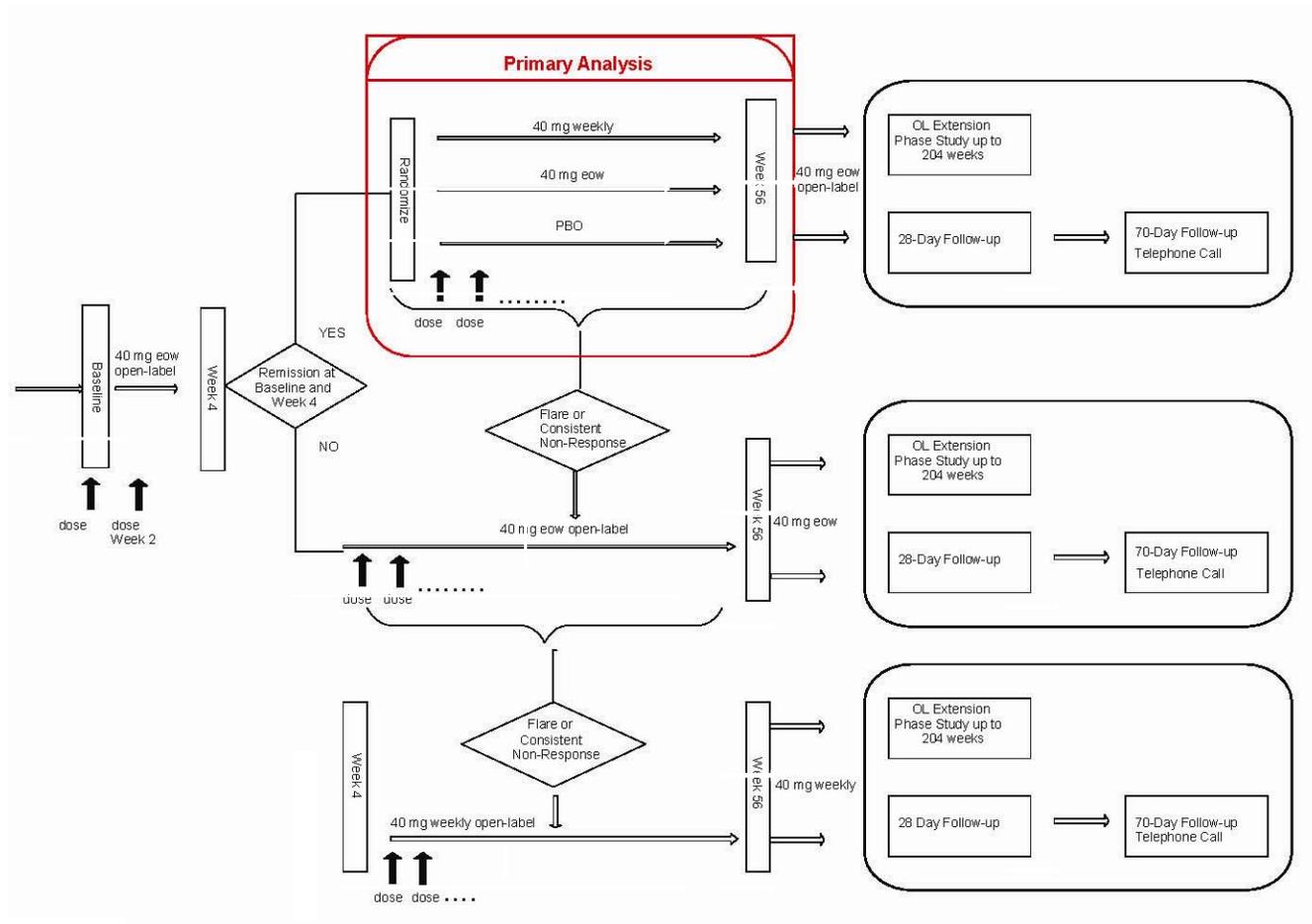
In addition to the systematic review, a number of supplemental issues were extensively considered and reported within a seven-page supplemental issue section.

Issues included:

- remission rate subgroup analyses
- information on comparator medications
- validity of outcome measures employed in the reviewed trials (Appendix III).

## APPENDIX II: CLASSIC II AND CHARM SCHEMATICS

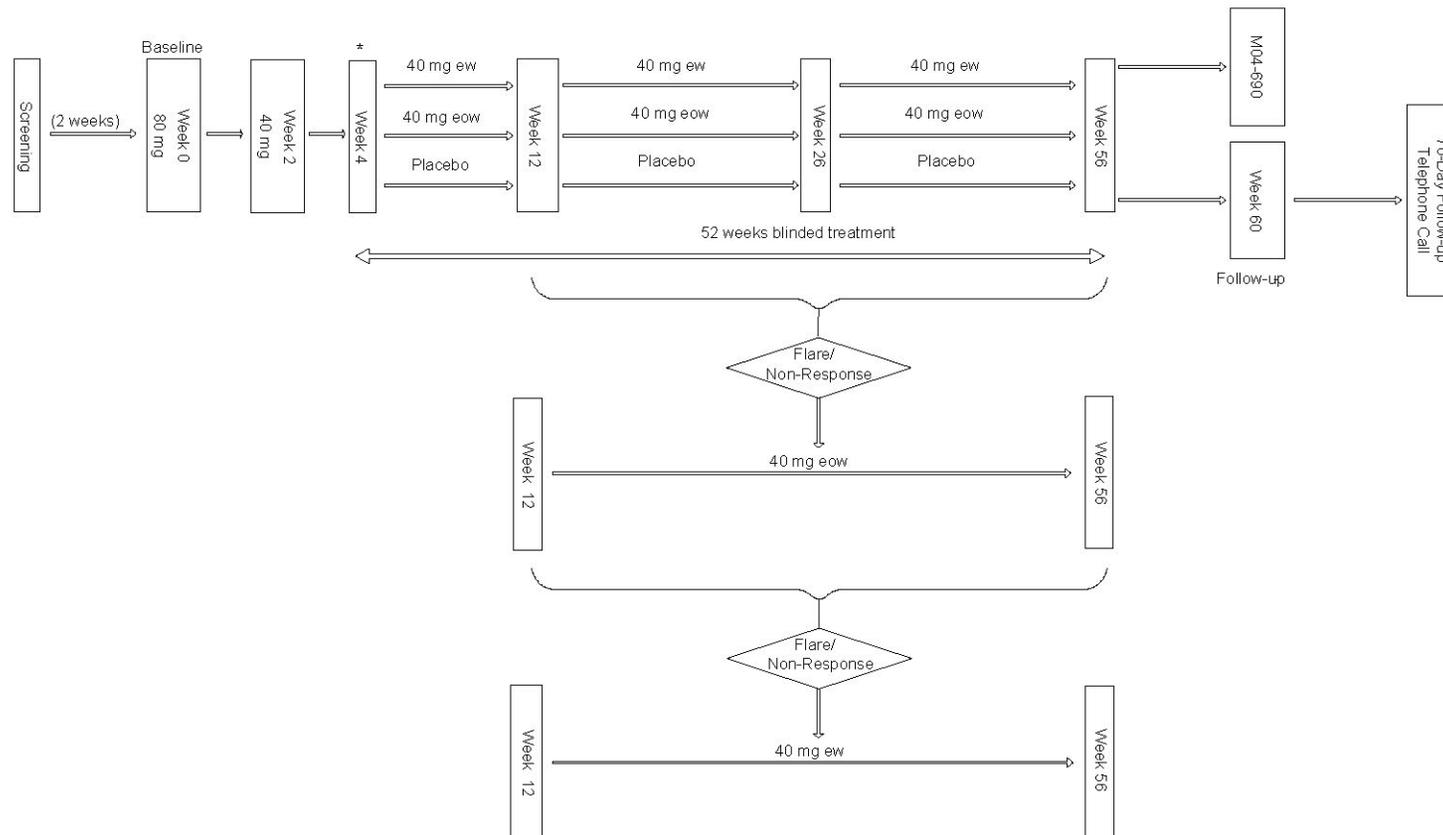
Study Schematic for the CLASSIC II Trial (source: manufacturer's submission binder)<sup>17</sup>



eow=every other week  
 OL=open label  
 PBO=placebo

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## Study Schematic for the CHARM Trial (source: manufacturer's submission binder)<sup>17</sup>



ew=every week  
eow=every other week  
M04-690=long term safety and tolerability study

## APPENDIX III: OUTCOME MEASURES

### Crohn's Disease Activity Index (CDAI)

- CDAI was developed by the National Cooperative Crohn's Disease Study group (NCCDS). It is based on the data collected prospectively from 187 visits of 112 patients with Crohn's disease.<sup>49</sup>
- CDAI is a disease-specific index that is generally accepted as the standard index for the assessment of Crohn's disease activity. The CDAI evaluates the activity of Crohn's disease in eight domains, sums up the weighted value of each item of the domain, and quantifies the global disease severity in a final numerical score.<sup>50</sup> (Appendix III, Table 1)

Table 1: Final Items Included in the CDAI and the Respective Weights	
Item (daily sum per week)	Weight
Number of liquid or very soft stools	2
Abdominal pain score in one week (rating:0 to 3)	5
General well-being (rating:0 to 4)	7
Sum of findings per week: <ul style="list-style-type: none"> <li>• Arthritis/arthralgia</li> <li>• Mucocutaneous lesions (e.g. erythema nodosum aphthous ulcers)</li> <li>• Iritis/uveitis</li> <li>• Anal disease (e.g., fissure, fistula)</li> <li>• External fistula (e.g., enterocutaneous, vesicle, vaginal)</li> <li>• Fever &gt;37.8°C</li> </ul>	20
Antidiarrheal use (e.g., diphenoxylate hydrochloride)	30
Abdominal mass (none=0, equivocal=2, present=5)	10
47 minus hematocrit (males) or 42 minus hematocrit (females)	6
100 x [1-(body weight divided by standard weight)]	1

- The CDAI is calculated using the patient's diary data, collected for seven days before each visit. The scores range from 0 to approximately 600. A score of 150 was defined as the cut-off between remission and active disease, scores of 150 to 219 as mildly active disease, scores of 220 to 450 as moderately active disease, and a value of 450 points was defined as the cut-off between active and very severe disease.<sup>51</sup>
- While unused in clinical practice, the CDAI is employed in most clinical trials of Crohn's disease.
- The minimum clinically important difference in the CDAI has not been established.<sup>51,52</sup> Most studies have defined remission as a CDAI score of <150 points, which is recommended as the primary endpoint, while response to treatment of active disease (i.e., a reduction in signs and symptoms), which is defined as a reduction in the CDAI score  $\geq 70$  to 100 points, is recommended as a secondary endpoint for the therapeutic trials.
- The CDAI demonstrated acceptable reliability and appears to be a valid instrument of assessment of the disease activity, although it is not appropriate for all patient subgroups and does not cover all domains of the Crohn's disease spectrum. It appears to correlate with physicians' assessments of disease severity, but the correlation of the CDAI with diagnostic markers of mucosal inflammation is inconsistent, which may reflect the global effects of Crohn's disease on patients.

## Inflammatory Bowel Disease Questionnaire (IBDQ)

- The IBDQ was developed based on the data collected from 97 patients with inflammatory bowel disease (IBD).<sup>53,54</sup>
- The final IBDQ is a 32-item questionnaire, including 10 questions relating to bowel symptoms, five questions relating to systemic symptoms, 12 questions relating to emotional function, and five questions relating to social function.
- Responses are graded on a 7-point Likert scale, with 7 denoting no problem at all and 1 denoting a very severe problem.
- The total IBDQ score is computed as the sum of the response to the individual IBDQ questions and ranges from 32 to 224, with a higher score indicating better quality of life. The scores of patients in remission usually range from 170 to 190.<sup>20,48,51,54-56</sup>
- No studies have defined the minimal change of score that represents clinical significance.
- The IBDQ can be self-administered and a shortened 10-question version has been validated.<sup>54</sup>
- The IBDQ is not used routinely in clinical practice, but has been used extensively as a secondary endpoint in clinical trials and correlated with health utility states in patients with Crohn's disease.<sup>51</sup>
- The IBDQ is a validated scale that measures quality of life in Crohn's patients and highly correlates with the CDAI score.

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