CADTH CANADIAN DRUG EXPERT COMMITTEE
FINAL RECOMMENDATION

INFLIXIMAB
(Inflectra — Hospira Healthcare Corporation)
Indications: Crohn Disease and Ulcerative Colitis

Please refer to the CADTH Canadian Drug Expert Committee (CDEC) recommendation dated December 19, 2014 for the reimbursement recommendation for Inflectra for the previously approved Health Canada indications — ankylosing spondylitis, rheumatoid arthritis, psoriatic arthritis, and plaque psoriasis.

Recommendation:
CDEC recommends that Inflectra (infliximab subsequent entry biologic [SEB]) be reimbursed in accordance with the Health Canada–approved indications for the treatment of Crohn disease (CD), fistulizing Crohn disease (FCD), and ulcerative colitis (UC), if the following clinical criterion and conditions are met:

Clinical Criterion:

- For use in patients for whom infliximab is considered to be the most appropriate treatment option.

Conditions:

- Reimburse in a manner similar to Remicade.
- The cost of treatment with Inflectra should provide a significant cost savings for jurisdictions compared with the cost of treatment with Remicade.

Reasons for the Recommendation:

1. Similarity between Inflectra and the reference product (Remicade) was established in two previously reviewed clinical trials in patients with rheumatoid arthritis (RA) and ankylosing spondylitis (AS) (PLANET-RA and PLANET-AS).
2. Extrapolation of the data from RA and AS to CD, FCD, and UC was granted by Health Canada on the basis of similarity between Inflectra and Remicade in patients with RA and AS, and newly submitted physiochemical and biological data.
3. The results of one ongoing phase IV, open-label, single arm, post-marketing surveillance study (CT-P13 PMS) suggested that there were no efficacy, safety, or tolerability concerns for patients with CD, FCD, and UC who were treated with Inflectra.

4. At the submitted price ($525.00 per 100 mg vial), Inflectra is less costly than Remicade ($987.56 per 100 mg vial) for use in accordance with the Health Canada–approved indications for the treatment CD, FCD, and UC.

Background:
Inflectra is an infliximab SEB based on Remicade as a reference product. It was approved by Health Canada in January 2014 for the following indications:

- Use in combination with methotrexate for a reduction in signs and symptoms, inhibition of the progression of structural damage, and an improvement in physical function in adult patients with moderately to severely active RA.
- Reduction of signs and symptoms and improvement in physical function in patients with active AS who have responded inadequately, or are intolerant to, conventional therapies.
- Reduction of signs and symptoms, induction of major clinical response, and inhibition of the progression of structural damage of active arthritis, and improvement in physical function in patients with psoriatic arthritis (PsA).
- Treatment of adult patients with chronic, moderate to severe plaque psoriasis (PsO) who are candidates for systemic therapy. For patients with chronic, moderate PsO, Inflectra should be used after phototherapy has been shown to be ineffective or inappropriate.

Inflectra was subsequently approved by Health Canada in June 2016 for the following indications, which are the indications under review for this recommendation:

- Reduction of signs and symptoms, induction and maintenance of clinical remission and mucosal healing, and reduction of corticosteroid use in adult patients with moderately to severely active CD who have had an inadequate response to a corticosteroid and/or an aminosalicylate. Inflectra can be used alone or in combination with conventional therapy.
- Treatment of FCD, in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment.
- Reduction of signs and symptoms, induction and maintenance of clinical remission and mucosal healing, and reduction or elimination of corticosteroid use in adult patients with moderately to severely active UC who have had an inadequate response to conventional therapy (i.e., an aminosalicylate and/or a corticosteroid, and/or an immunosuppressant).

Inflectra is available as a 100 mg/vial powder for solution, administered as an intravenous infusion. For the inflammatory bowel disease (IBD) indications, Health Canada's–approved dose is 5 mg/kg to 10 mg/kg.

Submission History:
Inflectra was previously reviewed by CDEC for the treatment of RA, AS, PsA, and PsO and received a recommendation to "list" with conditions (see Notice of CDEC Final Recommendation, December 19, 2014).

The original CADTH Common Drug Review (CDR) of Inflectra included two pivotal clinical trials:

- PLANET-RA (N = 606) was a phase III, randomized, double-blind, parallel-group, clinical equivalence study to compare the efficacy and safety of Inflectra and Remicade in adult patients with active RA.
- PLANET-AS (N = 250) was a phase I, randomized, double-blind, parallel-group study to compare the pharmacokinetics, safety, and efficacy of Inflectra and Remicade in adult patients with active AS.

CDEC recommended that Inflectra be listed for RA and AS based on the demonstration of similar efficacy, safety, and pharmacokinetics in these clinical trials and its lower cost compared with Remicade. CDEC also recommended that Inflectra be listed for PsO and PsA based on extrapolation of data from PLANET-RA and PLANET-AS.

Summary of CDEC Considerations:
CDEC considered the following information prepared by CDR: a review of manufacturer-provided information on clinical efficacy, safety, biosimilarity, and extrapolation of data for Inflectra; a review and critique of the manufacturer's pharmacoeconomic evaluation; and patient group–submitted information about outcomes and issues important to patients.

Patient Input Information
The following is a summary of key information provided by two patient groups (The Gastrointestinal Society and Crohn's and Colitis Canada) that responded to the CDR call for patient input. CDEC heard the following:

- Patients report being constantly concerned about disease flare-ups, which occur unpredictably. Limitations in leisure activities, physical activities, use of public transportation, and work were reported. Sustained remission or treatment response, therefore, is desired.
- The course of IBD is often unpredictable and differs from patient to patient; thus, treatment must be individualized. The availability and choice of different treatments options are important.
- Patients hope that treatment will improve quality of life, relieve symptoms, alleviate anxiety and stress, and allow them to lead normal lives in respect to family, career/education, and without interruptions due to flare-ups. They want each drug to be proven safe and effective, specifically in IBD.
- Of those aware of SEBs, patients expect SEBs to be clinically tested in Canadians for all indications, and to be subjected to a rigorous review and approval process.
- Patients expressed concerns about the following:
    - the safety and efficacy of SEBs
    - the regulatory process for approving these drugs in Canada
    - switching between the reference product and the SEB, especially without their consent. It was important to patients that they get to choose with the physician (not chosen by a government or drug plan) the best drug for their condition.
- Patients do not want cost to be the only consideration when deciding which biologic to use.

Clinical Evidence
The manufacturer provided efficacy data from one key clinical study.

Note: CT-P13 refers to the infliximab SEB (marketed as Inflectra in Canada).

CT-P13 PMS (post-marketing surveillance) (N = 173) is an ongoing (four year) phase IV, open-label, single arm observational study of CT-P13 for all approved indications in South Korea. An interim analysis was conducted in adults with moderately to severely active CD (N = 83), FCD (N = 12), and moderately to severely active UC (N = 78) across 15 study centres in South Korea, with a follow-up of 30 weeks. Most patients (N = 113) were infliximab treatment-naive and 60 patients were switched from the reference product, Remicade. CT-P13 was administered every 8 weeks (± 5 days) after induction therapy of three 5 mg/kg doses at weeks

0, 2, and 6. Doses of 5 mg/kg to 10 mg/kg were administered to 41% of patients. The study is limited by an uncontrolled observational design, small sample size, absence of important efficacy outcomes (e.g., extra-intestinal manifestations, disease biomarkers, quality of life, and immunogenicity), and short duration of follow-up (30-week interim analysis). The generalizability of the observed outcomes in patients from South Korea to Canadian patients with IBD is uncertain.

Other lines of evidence for the use of Inflectra in CD and UC:

- CT-P13 4.1 is a small (N = 20) phase IV, ongoing (four year), open-label, single arm study conducted in treatment-naive, adult patients with CD or UC in South Korea. An interim analysis in 10 patients ([redacted]) was available.
- Non-Celltrion sponsored studies — The manufacturer conducted a systematic search to identify non–Celltrion-sponsored studies that evaluated the use of CT-P13 in IBD. Six observational studies in adult patients were identified.
- Safety Evaluation Plan — The manufacturer conducted a systematic literature search of randomized controlled trials and observational studies of the reference product, Remicade, in patients with CD and UC. Rates of infusion-related reactions, infections, pneumonia, tuberculosis, malignancies, and need for surgery or hospitalization were compared with rates from observational studies of infliximab. The interpretation of this data is limited due to differences in study design, study populations, and outcome definitions.

Outcomes

CDEC discussed the following outcomes:

- Clinical response — defined as a reduction of at least 50% from baseline in the number of draining fistulas for patients with FCD; a ≥ 25% and ≥ 70 points decrease in Clinical Disease Activity Index (CDAI) score from baseline scores for patients with CD; and a decrease in partial Mayo scores from baseline of at least 2 points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point or an absolute subscore for rectal bleeding of 0 or 1 for patients with UC.
- Clinical remission — defined as the absence of draining fistulas for patients with FCD; CDAI score of < 150 for patients with CD; a total partial Mayo score of 2 points or lower, with no individual subscore exceeding 1 point for patients with UC.
- Disease control — defined as the exclusion of loss of response cases from disease control for patients with FCD; the exclusion of disease worsening cases from disease control for patients with CD and UC.
- Rescue medication — defined as any concomitant medication that was started after the first infusion date to treat new or unresolved symptoms of CD or UC.
- Mucosal healing — defined as Mayo endoscopic subscore of ≤ 1 point for patients with UC.
- Adverse events and serious adverse events.

The primary outcome in CT-P13 PMS was not stated.

Efficacy

CT-P13 PMS

Based on last observation carried forward imputation:

- Among CD infliximab-naive patients, 31/39 (79.5%) achieved clinical response and 23/39 (59.0%) achieved clinical remission at week 30.
- Among CD patients who were switched from Remicade to CT-P13, 25/31 (80.6%) achieved remission from visits two to six and 27/31 (87.1%) of patients did not experience disease worsening. Rescue medication was needed by 9/40 (22.5%).
- Among FCD infliximab-naive patients, 2/6 (33.3%) achieved clinical response and 1/6 (16.7%) achieved clinical remission.
- Among FCD patients switched from Remicade to CT-P13, clinical remission and disease control were achieved in one patient at visit six (data were available for only one patient).
- In UC infliximab-naive patients, 39/54 (72.2%) achieved clinical response and 20/54 (37.0%) achieved clinical remission at week 30.
- Among UC patients who were switched from Remicade to CT-P13, 5/11 (45.5%) achieved remission throughout visits two to five and no patients experienced disease worsening.

Based on a complete case analysis:

- Among UC infliximab-naive patients, 9/13 (69.2%) experienced mucosal healing at week 30 while 6/9 (66.7%) patients who were switched from Remicade to CT-P13 experienced mucosal healing throughout visits 2 to 5.

Harms (Safety and Tolerability)

CT-P13 PMS

- A total of 51 treatment-emergent adverse events (TEAEs) in 38 patients occurred.
  - In patients with CD, 19 events occurred in 15/83 patients (18.1%).
  - In patients with FCD, 2 events occurred in 2/12 patients (16.7%).
  - In patients with UC, 30 events occurred in 21/78 patients (26.9%).
- There were no notable differences in TEAEs between patients who were infliximab-naive (23.9%) and those switched from Remicade (18.3%).
- There were no notable dose-dependent differences in distribution of TEAEs between patients who received doses of 5 mg/kg or > 5 mg/kg.
- Infusion-related reactions (IRR), including hypersensitivity and anaphylaxis, were reported in 9 patients (5.2%).
- One patient (0.6%) had active tuberculosis after infliximab exposure.
- No malignancies, pneumonia, deaths, or any other events of special interest were observed during the 30-week interim period.

Other lines of evidence for the use of Inflectra in CD and UC

CT-P13 4.1

- [redacted]
- [redacted]
- [redacted]

Safety Evaluation Plan

- Safety data were generally similar between CT-P13 and Remicade in treatment-naive and switched patients combined for IRRs, pneumonia, tuberculosis, and malignancies. There were some differences in the rates of infection, surgery, and disease-related hospitalization.

Extrapolation

Inflectra was originally approved in Canada for PsO and PsA based on extrapolation of evidence from patients with RA and AS, given the similarities in pathology and mechanisms of action of tumour necrosis factor (TNF) alpha blockers in these indications. When originally approved, Health Canada did not support extrapolating from RA and AS to IBD due to differences in disease mechanisms (role of transmembrane TNF alpha and antibody-dependent cell-mediated cytotoxicity in IBD) and safety profiles of infliximab in IBD verses rheumatic diseases (higher risk of hepatosplenic T-cell lymphoma in IBD). In June 2016, Health Canada approved Inflectra for the adult IBD indications stating that the approval was based on previously submitted clinical studies that demonstrated comparable efficacy and safety in patients with RA and comparable pharmacokinetics in patients with AS, newly submitted physiochemical and biological data, and rationales addressing the potential mechanisms of action and their relationships to clinical outcomes in IBD.

Cost and Cost-Effectiveness

The manufacturer submitted a cost comparison between Inflectra and Remicade for the indications reviewed. As validated by CDR, the manufacturer-submitted price of Inflectra ($525.00 per 100 mg vial) is 47% less than that of Remicade when using the price obtained for Remicade from the Ontario Drug Benefit Exceptional Access Program ($987.56 per 100 mg vial).

CDR identified the following issues for consideration:

- The clinical expert noted that physicians and patients may be reluctant to switch from Remicade to Inflectra when a patient is adequately managed on Remicade. As a result, it may be more likely that Inflectra is used in patients who are new to infliximab rather than those switching from Remicade.
- The manufacturer of Remicade sponsors infusion centres for the administration of Remicade, and covers costs of patient follow-up and monitoring. These costs are expected to be similarly covered by the manufacturer of Inflectra; therefore, this is not expected to result in additional costs to the publicly funded health care system.
- The reimbursement criteria for Remicade differ across publicly funded drug plans in Canada. The expected savings from Inflectra compared with Remicade are based on the assumption that the reimbursement criteria for Remicade would be applied to Inflectra.

Other Discussion Points:

- CDEC noted that there were no currently available reported studies directly comparing Inflectra with Remicade for patients with IBD. One study (CT-P13 3.4) is an ongoing phase III randomized, double-blind, parallel-group, efficacy, and safety study designed to demonstrate non-inferiority of CT-P13 to Remicade in adults during a 54-week period, and plans to enrol 214 patients. An interim analysis at week 14 focusing on the development of anti-drug antibodies suggests similarity between the two groups.

CDEC Members:
Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeysundera.

September 21, 2016 Meeting

Regrets:
Three CDEC members did not attend.

Conflicts of Interest:
None

About this Document:
CDEC provides formulary reimbursement recommendations or advice to CDR participating drug plans.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*. CADTH has redacted the requested confidential information in accordance with the CDR Confidentiality Guidelines.

The CDEC recommendation or record of advice neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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