



## CDEC FINAL RECOMMENDATION

### INFLIXIMAB

(Inflectra — Hospira Healthcare Corporation)

**Indications: Rheumatoid Arthritis, Ankylosing Spondylitis, Psoriatic Arthritis, Plaque Psoriasis**

#### **Recommendation:**

The Canadian Drug Expert Committee (CDEC) recommends that Inflectra (infliximab subsequent entry biologic [SEB]) be listed in accordance with the Health Canada–approved indications for the treatment of rheumatoid arthritis, ankylosing spondylitis, plaque psoriasis, and psoriatic arthritis, if the following conditions are met:

#### **Conditions:**

- For use in patients for whom infliximab is considered to be the most appropriate treatment option.
- List in a manner similar to Remicade.

#### **Reasons for the Recommendation:**

1. Two randomized controlled trials (RCTs) demonstrated that Inflectra and Remicade have similar efficacy, safety, and pharmacokinetic (PK) profiles in patients with rheumatoid arthritis (PLANET-RA; N = 606) and ankylosing spondylitis (PLANET-AS; N = 250).
2. Extrapolation of the data from rheumatoid arthritis and ankylosing spondylitis to psoriatic arthritis and psoriatic plaques is supported by the similar pathophysiology of these conditions and the identical dosage regimen for infliximab for these indications.
3. At the submitted price (\$650.00 per 100 mg vial), Inflectra is less costly than Remicade (\$987.56 per 100 mg vial) for the treatment of rheumatoid arthritis, ankylosing spondylitis, psoriatic plaques, and psoriatic arthritis.

#### **Of Note:**

CDEC noted that several comparators used for the treatment of rheumatoid arthritis, ankylosing spondylitis, plaque psoriasis, and psoriatic arthritis are less costly than Inflectra.

### **Background:**

Inflectra is an infliximab SEB based on Remicade as a reference product. It has been approved in Canada for the following indications:

- Use in combination with methotrexate for reduction in signs and symptoms, inhibition of the progression of structural damage, and improvement in physical function in adult patients with moderately to severely active rheumatoid arthritis.
- Reduction of signs and symptoms and improvement in physical function in patients with active ankylosing spondylitis 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.
- Treatment of adult patients with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy. For patients with chronic moderate plaque psoriasis, Inflectra should be used after phototherapy has been shown to be ineffective or inappropriate.

In contrast to Remicade, Inflectra is not approved for the treatment of Crohn disease or ulcerative colitis.

### **Summary of CDEC Considerations:**

CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a review of manufacturer-provided information on the clinical efficacy, biosimilarity, and extrapolation of data for Inflectra; a 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 six patient groups that responded to the CDR call for patient input:

- Therapeutic options are required for patients who live with arthritis, and SEBs offer another biologic drug therapy that may be effective for patients who are biologic-naive or who have failed on other biologic drugs. Many patients are uncertain, however, about whether an SEB actually offers an additional therapeutic option.
- Some patients expect that Inflectra will be considerably less costly than the reference product and will therefore lower health care costs and potentially increase access to treatment.
- Patients expressed concern about the following:
  - Patient support programs are an important part of biologic therapies and patient groups are unclear whether manufacturers of SEBs will offer them.
  - Inflectra and Remicade have the same non-proprietary name (i.e., infliximab) and patients are concerned about being inadvertently exposed to the wrong drug or being "switched" to the SEB without their knowledge or consent.
  - Some patient groups were uncertain whether the SEB will work as well as the reference product, whether it was tested as rigorously, and whether it was or will be manufactured as carefully.

### **Clinical Trials**

The manufacturer provided efficacy data from two pivotal clinical trials:

- PLANET-RA (N = 606) was a phase 3, randomized, double-blind, multi-centre, multinational, parallel-group clinical equivalence study designed to compare the efficacy and safety of Inflectra with Remicade, in patients with active rheumatoid arthritis who had an inadequate response to treatment with methotrexate. The primary end point was the proportion of patients with an American College of Rheumatology (ACR) 20 response at week 30. Therapeutic equivalence of clinical response according to ACR20 criteria would be demonstrated if the 95% confidence interval (CI) for the treatment difference was within  $\pm 15\%$ .
- PLANET-AS (N = 250) was a phase 1, randomized, double-blind, multi-centre, multinational, parallel-group study designed to compare the PK, safety, and efficacy of Inflectra and Remicade, in patients with active ankylosing spondylitis. The primary end point was to demonstrate PK equivalence at a steady state of area under the concentration-time curve and observed maximum steady state serum concentration between Inflectra and Remicade between weeks 22 and 30. Equivalence was demonstrated if the 90% CIs lay within the equivalence margin of 80% to 125%.

### **Outcomes**

CDEC discussed the following outcomes:

- ACR 20 response rate — defined as the proportion of patients achieving 20% improvement in tender and swollen joint counts and 20% improvement in three of the five remaining ACR core set measures: patient pain assessment (measured by visual analogue scale [VAS]), patient global assessment (measured by VAS), physician global assessment (measured by VAS), patient self-assessed disability (measured by Health Assessment Questionnaire), and acute-phase reactant (erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP]).
- ACR 50 and ACR 70 — similar to the ACR 20, but with improvements of 50% and 70%.
- Disease Activity Score 28 (DAS 28) — a measure of disease activity that takes into consideration the 28-joint counts of tenderness and swelling, plus the ESR or CRP, and a general health assessment scored on a VAS. Scores of less than 2.6 are considered to be remission, and a score greater than 5.1 is considered to be high disease activity.
- European League Against Rheumatism (EULAR) response criteria — classification of disease state based on the DAS 28 scale.
- ASAS 20 response — defined as an improvement of at least 20% and an absolute improvement of at least 10 units on a 0 to 100 scale, or 1 unit on a 0 to 10 scale from baseline in at least three of the following domains: patient global assessment of disease status; patient assessment of spinal pain; function according to the Bath Ankylosing Spondylitis Functional Index; morning stiffness determined using the last two questions of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Additionally, ASAS 20 responders should not have deterioration (worsening of at least 20% and an absolute worsening of at least 10 units on a 0 to 100 scale or 1 unit on a 0 to 10 scale) of the remaining assessment domain relative to baseline.
- ASAS 40 response — defined as an improvement of at least 40% and an absolute improvement of at least 2 units on a 0 to 10 scale from baseline in at least three of the four domains of the ASAS 20, with no deterioration from baseline in the remaining domain.
- Serious adverse events, total adverse events, and withdrawals due to adverse events.

**Efficacy**

Rheumatoid Arthritis (PLANET-RA)

- The proportion of patients achieving an ACR 20 response at week 30 was similar in the Inflectra group (60.9%) and the Remicade group (58.6%). The difference of proportions between the groups was 2% (95% CI, -6% to 10%) in the intention-to-treat (ITT) analysis and 4% (95% CI, -4% to 12%) in the per-protocol (PP) analysis. The 95% CIs for the treatment difference were contained within the pre-determined equivalence range of  $\pm 15\%$  for both ITT and PP analyses.
- The proportion of patients who demonstrated ACR50 and ACR70 responses was similar between the Inflectra and Remicade groups, with treatment differences reported as follows:
  - ACR 50: 2% (95% CI, -6% to 9%) at week 30 and week 54.
  - ACR 70: 1% (95% CI, -5% to 7%) at week 30 and week 54.
- The changes in DAS28 scores were similar between the Inflectra and Remicade groups regardless of whether the measure included CRP or ESR. The least square mean difference between Inflectra and Remicade was reported as follows:
  - DAS 28 (ESR): [REDACTED]
  - DAS 28 (CRP): [REDACTED]
- There were no statistically significant differences between the Inflectra and Remicade groups for the proportion of patients achieving moderate or good responses for both EULAR (ESR) and EULAR (CRP) measures. The odds ratios for achieving moderate or good responses were as follows:
  - EULAR (ESR): [REDACTED]
  - EULAR (CRP): [REDACTED]

Ankylosing Spondylitis (PLANET-AS)

- A similar proportion of patients in the Inflectra and Remicade groups demonstrated ASAS 20 and ASAS 40 responses at weeks 14, 30, and 54. There were no statistically significant differences between the two treatment groups, with odds ratios reported as follows:
  - ASAS 20: 0.91 (95% CI, 0.53 to 1.54) at week 14; 0.91 (95% CI, 0.51 to 1.62) at week 30; and 0.89 (95% CI, 0.50 to 1.59) at week 54.
  - ASAS 40: 0.85 (95% CI, 0.51 to 1.42) at week 14; 1.19 (95% CI, 0.70 to 2.00) at week 30; and 1.26 (95% CI, 0.73 to 2.15) at week 54.

**Harms (Safety and Tolerability)**

- The proportion of patients who reported at least one serious adverse event was:
  - PLANET-RA: 13.9% with Inflectra and 10.0% with Remicade.
  - PLANET-AS: [REDACTED]% with Inflectra and [REDACTED]% with Remicade.
- The proportion of patients who reported at least one adverse event was:
  - PLANET-RA: 70.2% with Inflectra and 70.3% with Remicade.
  - PLANET-AS: 72.7% with Inflectra and 67.2% with Remicade.
- The proportion of patients with at least one infection was:
  - PLANET-RA: [REDACTED]% with Inflectra and [REDACTED]% with Remicade.
  - PLANET-AS: [REDACTED]% with Inflectra and [REDACTED]% with Remicade.

- The proportion of patients who withdrew as a result of adverse events was:
  - PLANET-RA: █% with Inflectra and █% with Remicade.
  - PLANET-AS: █% with Inflectra and █% with Remicade.

### **Extrapolation**

Health Canada granted the extrapolation of data from the manufacturer's studies in rheumatoid arthritis (PLANET-RA) and ankylosing spondylitis (PLANET-AS) to the indications of plaque psoriasis and psoriatic arthritis. Health Canada stated that the indications for psoriatic arthritis and plaque psoriasis were granted on the basis of similarity and the absence of meaningful differences between Inflectra and Remicade with respect to quality, mechanism of action, disease pathophysiology, safety, dosage regimen, and on clinical experience with the reference product (i.e., Remicade). The manufacturer had also requested extrapolation to Crohn disease and ulcerative colitis; however, Health Canada did not grant those indications for Inflectra, noting that the differences between Inflectra and Remicade could have an impact on the clinical safety and efficacy in those patient populations.

### **Cost and Cost-Effectiveness**

The manufacturer submitted a cost comparison of Inflectra with Remicade for the four indications under review: rheumatoid arthritis, ankylosing spondylitis, plaque psoriasis, and psoriatic arthritis. The cost of Inflectra (\$650 per 100 mg vial) is 34.2% less costly than Remicade when using the Ontario Exceptional Access Program (EAP) price of Remicade (\$987.56 per 100 mg vial).

CDR identified the following issues for consideration:

- Inflectra can be used either for patients who would otherwise have initiated Remicade or other biologic disease-modifying antirheumatoid drugs (bDMARDs). Compared with other, less expensive bDMARDs, Inflectra would result in an incremental cost.
- Some drug plans have a lower list price than Ontario EAP for Remicade and, as such, the expected savings with Inflectra may vary across the CDR-participating drug plans. Furthermore, the projected savings do not account for any product listing agreements for Remicade.
- For patients who have an incomplete response with infliximab, consideration may be given to adjusting the dose up to 10 mg/kg and/or treating as often as every four weeks. Dose escalation would affect both Inflectra and Remicade, not affecting the relative cost difference. However, this would have a considerable impact when comparing the cost of Inflectra with other bDMARDs.
- The dosage of infliximab is based on a patient's body weight, and the manufacturer's comparisons for rheumatology indications were based on an average weight of 70 kg. Inflectra and Remicade share the same dosing strategies, and variations in body weight would not affect the relative cost difference between the two; however, this would have an impact when Inflectra is compared with other bDMARDs.
- The indications under review are chronic in nature. The relative cost of Inflectra compared with Remicade is not expected to vary with a longer time horizon, but this would affect the comparison with other bDMARDs, due to the loading doses used in the first year for some biologic therapies.

In addition to the issues above, the recommended dose for each indication will also affect the relative cost of Inflectra compared with Remicade and other bDMARDs:

- For rheumatoid arthritis, for the first year of treatment, assuming a weight of 70 kg, Inflectra (3 mg/kg, \$15,600) is less costly than Remicade (3 mg/kg, \$23,701) and all other bDMARDs (range: \$15,680 to \$20,207), except for low-dose intravenous tocilizumab 4 mg/kg (\$8,153) and subcutaneous tocilizumab every other week (\$10,014). If the dose of infliximab is increased to 5 mg/kg or 10 mg/kg, or the frequency of injection is increased to every four weeks during the first year, Inflectra may become more costly than most other bDMARDs.
- For ankylosing spondylitis, for the first year of treatment, Inflectra (5 mg/kg, \$20,800) is less costly than Remicade (5 mg/kg, \$31,601) but more costly than all other bDMARDs (range: \$18,243 to \$20,207).
- For psoriatic arthritis, for the first year of treatment, Inflectra (5 mg/kg, \$20,800) is less costly than Remicade (5 mg/kg, \$31,601) and ustekinumab (\$22,966), but more costly than all other bDMARDs (range: \$18,243 to \$20,207).
- For plaque psoriasis, for the first year of treatment (using Saskatchewan Formulary costs, as Ontario EAP does not routinely reimburse bDMARDs for this indication), Inflectra (5 mg/kg, \$20,800) is less costly than Remicade (5 mg/kg, \$31,232), etanercept (\$25,001 to \$25,008), and ustekinumab (\$22,966), but is more costly than adalimumab (\$20,730).

### Other Discussion Points:

- At the submitted price, Inflectra is less costly than Remicade; however, it is more costly than other bDMARDs approved for use in the same indications.
- Listing status for Remicade varies across the CDR-participating drug plans.

### Research Gaps:

- There are no controlled clinical trials evaluating the safety and efficacy of Inflectra in the treatment of plaque psoriasis or psoriatic arthritis.
- There are limited data regarding the long-term efficacy and safety of Inflectra in any of the indicated patient populations.

### 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, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

### November 19, 2014 Meeting

#### Regrets:

None

#### Conflicts of Interest:

None

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## Common Drug Review

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