CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

INFLIXIMAB (RENFLEXIS — Samsung Bioepis Co., Ltd., Distributed by Merck Canada)

Indications: Rheumatoid Arthritis, Ankylosing Spondylitis, Crohn's Disease (adult and pediatric), Fistulising Crohn's Disease, Ulcerative Colitis (adult and pediatric), Psoriatic Arthritis, Plaque Psoriasis.

RECOMMENDATION:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that Renflexis (infliximab biosimilar) be reimbursed in accordance with the Health Canada-approved indications for the treatment of rheumatoid arthritis, ankylosing spondylitis, adult and pediatric Crohn's disease, fistulising Crohn's disease, adult and pediatric ulcerative colitis, psoriatic arthritis, and plaque psoriasis, if the following criterion and condition are met:

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

Condition:
- The cost of treatment with Renflexis should provide significant cost savings for jurisdictions compared with the cost of treatment with existing infliximab products.

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

Condition:

- The cost of treatment with Renflexis should provide significant cost savings for jurisdictions compared with the cost of treatment with existing infliximab products.

Reasons for the Recommendation:

1. One phase I clinical trial in healthy subjects (Study SB2-G11-NHV; N = 159), and one phase III trial in patients with rheumatoid arthritis (Study SB2-G31-RA; N = 584) demonstrated that Renflexis has similar pharmacokinetics, efficacy, safety, and immunogenicity as the reference product, Remicade.
2. Extrapolation of the data from rheumatoid arthritis to ankylosing spondylitis, Crohn's disease, ulcerative colitis, psoriatic arthritis, and plaque psoriasis is reasonable given the demonstrated similarities between Renflexis and Remicade in the included trials, and the role that tumour necrosis factor alpha (TNF-alpha) drugs play in these indications.
3. At a manufacturer submitted price of $525.00 per vial (100 mg/vial lyophilized powder), Renflexis is less costly than Remicade based on the Ontario Public Drug Plan price ($987.56 per 100 mg vial of lyophilized powder) for use in accordance with the Health Canada-approved indications. Renflexis is the same price as Inflectra, the first infliximab biosimilar approved by Health Canada, based on the Ontario Public Drug Plan price ($525.00 per 100 mg vial of lyophilized powder).

Of Note:

- CDEC noted that Renflexis is the second infliximab biosimilar to be approved for use in Canada; however, it is the first infliximab biosimilar to be approved by Health Canada for the pediatric indications of the reference product, Remicade.
- CDEC noted that evidence regarding switching from Remicade to Renflexis was examined in the 24-week double-blind transition-extension phase of Study SB2-G31-RA. Although there were numerically higher instances of alanine aminotransferase (ALT) increases, latent tuberculosis (TB) cases, [redacted], these numerical differences were not statistically significant and not interpreted to be clinically significant. Hence, given the overall similarity in efficacy and safety, CDEC considered that a patient being treated with Remicade could be considered for switching to Renflexis following a discussion between the patient and his or her physician.

Background:

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

- Use in combination with methotrexate for the 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 and maintenance of clinical remission and mucosal healing and reduction of corticosteroid use in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to a corticosteroid and/or aminosalicylate. Renflexis can be used alone or in combination with conventional therapy.
- Reduction of signs and symptoms and induction and maintenance of clinical remission in pediatric patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy (corticosteroid and/or aminosalicylate and/or an immunosuppressant). The safety and efficacy of Renflexis is not established in patients younger than nine years of age.
- Treatment of fistulising Crohn's disease, 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 ulcerative colitis who have had an inadequate response to conventional therapy (i.e., aminosalicylate and/or corticosteroid and/or an immunosuppressant).
- Reduction of signs and symptoms, induction and maintenance of clinical remission, and induction of mucosal healing in pediatric patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy (i.e., aminosalicylate and/or corticosteroid and/or an immunosuppressant). The safety and efficacy of Renflexis have not been established in patients younger than six years of age.
- 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, Renflexis should be used after phototherapy has been shown to be ineffective or inappropriate. When assessing the severity of psoriasis, the physician should consider the extent of involvement, location of lesions, response to previous treatments, and impact of disease on the patient's quality of life.

The first infliximab biosimilar, Inflectra, was reviewed by CDEC and received a recommendation to reimburse with criteria and/or conditions in December 2014 for the indications of rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis, and in October 2016 for the indications of Crohn's disease and ulcerative colitis. Inflectra does not currently have Health Canada-approval for use in pediatric patients.

Summary of CDEC Considerations:

The Committee considered the following information prepared by the CADTH Common Drug Review (CDR): a review and critical appraisal of manufacturer-provided information on biosimilarity, an assessment of the manufacturer's cost comparison analysis, and patient group-submitted information about outcomes and issues important to patients and caregivers.

Patient Input Information

Two patient groups (Arthritis Consumer Experts [ACE] and The Arthritis Society) responded to the call for patient input for this CDR review. Information for the ACE submission was gathered from a call for patient experiences, work with clinical researchers in Canada, and discussions with the ACE advisory board; information for the Arthritis Society submission was gathered from a request for information on social media. Patients with rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis provided their perspectives; however, the perspectives of patients with Crohn's disease or ulcerative colitis were not available. The following is a summary of key input from the perspective of the patient groups:

- Patients indicated that the treatments for these conditions were often associated with troubling side effects. The efficacy often waned over time, requiring a change of treatment. Patients want to have as many treatment options available as possible, as this provides alternatives in the event of treatment failure, waning of efficacy over time, side effects, or lack of

coverage. Patients would also like to see treatments that confer better control of pain and fatigue, have fewer side effects, are less costly, and that are available in different administration routes.

- Patients discussed Remicade and one patient described the use of Inflectra. For some patients, infliximab has helped with symptom control and disease progression, but for others the treatment stopped working or had side effects. Although some side effects, such as tiredness and infusion-site reactions were manageable, patients also mentioned development of allergic reactions that required discontinuation of medication.
- Although the lower cost of biosimilars was welcomed by some, a need for more clinical trial data on the safety of biosimilars was also stated. Patient groups emphasized that a switch to a biosimilar should be made cautiously, especially if a patient has been stabilized for several years on the reference product. The decision to initiate or switch a medication should not be forced by insurers.

Clinical Trials

The manufacturer provided efficacy data from two pivotal clinical trials.

Study SB2-G11-NHV

Study SB2-G11-NHV is a phase I, randomized, three-arm, single-blind study, comparing Renflexis (N = 53) with EU-Remicade (N = 53) and US-Remicade (N = 53) in 159 healthy patients, mostly males (94%), from a single centre in Germany. A single dose of 5 mg/kg Renflexis, EU-Remicade, or US-Remicade was infused intravenously (IV) over 120 minutes and patients were followed for 10 weeks.

Study SB2-G31-RA

Study SB2-G31-RA is a phase III, randomized, double-blind, multinational (11 countries in Europe and Asia) study to evaluate the efficacy, safety, immunogenicity, and pharmacokinetics of Renflexis (N = 291) compared with EU-Remicade (N =293) in patients, majority female (80%), with moderate to severe rheumatoid arthritis despite methotrexate therapy. Patients were administered Renflexis or EU-Remicade at doses of 3 mg/kg IV at Weeks 0, 2, 6, then every 8 weeks thereafter, and received methotrexate 10 mg/week to 25 mg/week and folic acid 5 mg/week to 10 mg/week. Dose increases of Renflexis or Remicade were permitted by 1.5 mg/kg up to a maximum of 7.5 mg/kg. The initial study lasted for 54 weeks, and was followed by a 24-week double-blind transition-extension phase that included 68% of the original study population. In the transition-extension phase, patients from the EU-Remicade group were randomized to switch to Renflexis (N = 94) or remain on Remicade (N = 101), and patients who received Renflexis during the 54-week study continued with Renflexis during the transition phase (N = 201). The transition phase was added to the protocol after the study had already begun.

Outcomes

CDEC discussed the following outcomes:

- proportion of patients with American College of Rheumatology (ACR) 20 response at week 30: ACR 20 response was defined as: at least a 20% improvement from baseline in swollen joint count (66 joint count); at least a 20% improvement from baseline in tender joint count (68 joint count); and at least a 20% improvement from baseline in at least three of the following five criteria: subject pain assessment using a 100 mm visual analogue scale (VAS), patient global assessment using a 100 mm VAS, physician global assessment using a 100 mm VAS, patients assessment of disability using the Health Assessment Questionnaire — Disability Index (HAQ-DI), and acute phase reactant level (C-reactive protein [CRP])
- proportion of patients with ACR 20 response at week 54
- proportion of patients with ACR 50 and ACR 70 response at Week 30 and Week 54
- numeric index of the ACR response (ACR-N) at Week 30 and Week 54
- disease activity score based on a 28-joint count (DAS 28 score) at Week 30 and Week 54
- the European League Against Rheumatism (EULAR) response at Week 30 and Week 54
- major clinical response (ACR 70 response for six consecutive months) at Week 54
- change from baseline in modified Total Sharp Score (mTSS) at Week 54

- adverse events (AEs) and serious adverse events (SAEs)
- immunogenicity — anti-drug antibodies (ADA) and neutralizing antibodies (Nab)
- primary pharmacokinetic end points (maximum concentration [C_{max}], area-under-curve from time zero to infinity [AUC_{inf}] and from time zero to last quantifiable concentration [AUC_{last}]).

The primary end points of Study SB2-G11-NHV were pharmacokinetic (AUC_{inf}, AUC_{last}, C_{max}). The primary end points were considered met if the 90% confidence interval (CI) for the geometric mean was within the equivalence margin of 80% to 125%.

The primary end point of Study SB2-G31-RA was ACR 20 response at Week 30. The primary end point was considered met if the 95% CI of the adjusted treatment difference was within the equivalence margin of −15% to 15%.

Efficacy

Study SB2-G11-NHV:

The pharmacokinetics of Renflexis were similar to EU-Remicade and US-Remicade, as all parameters were within the pre-specified equivalence margin of 80% to 125%. When the pharmacokinetic analyses were stratified based on ADA-positive and ADA-negative status, the results remained within the equivalence margin.

The incidence of ADA formation was numerically higher in the Renflexis group, but not statistically significant:

- Day 29: Renflexis: 3.8%; EU-Remicade: 0%; US-Remicade: 1.9%
- Day 71: Renflexis: 47.2%; EU-Remicade: 37.7%; US-Remicade: 37.7%.

Study SB2-G31-RA (initial 54-week phase):

The proportion of patients achieving ACR 20 at week 30 was similar between the Renflexis group (55.5%) and the Remicade group (59.0%). The adjusted differences in proportions between the groups were –2.95% (95% CI, –10.88 to 4.97%) in the full analysis set, and –1.88% (95% CI, −10.26% to 6.51%) in the per-protocol set. The 95% CIs for the treatment difference were contained within the pre-determined equivalence margin of −15% to 15% for both the full analysis set and the pre-protocol set analysis.

The treatments were similar for ACR 20 at Week 54, ACR 50 at Weeks 30 and 54, and ACR 70 at Weeks 30 and 54. The treatments were also similar for other secondary outcomes: major clinical response, DAS 28 response, EULAR response, HAQ-DI, and mTSS.

Numerically more patients in the Renflexis group developed ADAs compared with EU-Remicade at Week 54: The percentage of patients who were ADA-positive for Renflexis was 62.4% versus 57.5% for EU-Remicade (*P* = 0.270).

Study SB2-G31-RA (24-week transition-extension phase):

ACR 20, ACR 50, and ACR 70 response rates were similar between groups and at each time point (Weeks 54, 62, 70, 78). DAS 28 mean changes from baseline to Week 78 and EULAR response were similar between groups.

For overall ADA (Week 0 up to 78), there was no statistically significant difference in ADA positivity: The percentage of patients who were ADA-positive was as follows: Renflexis/Renflexis group 66.2% versus Remicade/Renflexis group 62.8% versus Remicade/Remicade group 60.4%.

Harms (Safety and Tolerability)

Study SB2-G11-NHV:

No infusion-related reactions, serious infections, tuberculosis, malignancies, or deaths occurred in any group. There were numerical differences between groups in the occurrence of treatment-emergent AEs (TEAEs):

- at least one TEAE: Renflexis 50.9% (mostly mild); EU-Remicade 39.6%; US-Remicade 43.4%.
- TEAEs related to treatment: Renflexis 47.2%; EU-Remicade 26.4%; US-Remicade 26.4%
- the most frequently reported TEAEs suspected to be related to the study drugs were nasopharyngitis (Renflexis: 11.3%, EU-Remicade: 7.5% and US-Remicade: 5.7%) and headache (9.4%, 11.3%, and 13.2%).

There was one SAE of Borrelia infection, related to Renflexis, and no SAEs with the reference products

Study SB2-G31-RA (initial 54-week phase):

The incidence of infusion-related reactions was higher in ADA-positive patients (Renflexis: 5.2%; EU-Remicade: 3.8%) than in ADA-negative patients (Renflexis: 0.7%; EU-Remicade: 1.4%) at Week 54. However, the incidence was similar between the two treatment groups within each ADA subgroup.

Commonly occurring TEAEs included latent TB (Renflexis: 6.6%; Remicade: 7.2%), nasopharyngitis (Renflexis: 6.2%; Remicade: 6.8%), and alanine aminotransferase increase (Renflexis: 7.9%; Remicade: 3.1%)

There were more withdrawals due to AEs in the Renflexis group compared with EU-Remicade (7.2% versus 3.4% by Week 30 and 9.3% versus 7.2% by Week 54). Of 68 SAEs reported, one SAE in the Renflexis treatment group was of unknown outcome (non-malignant brain neoplasm related to study drug).

One death was reported in the EU-Remicade group (severe worsening of left ventricular failure - congestive heart failure).

Study SB2-G31-RA (24-week transition-extension phase):

Commonly occurring TEAEs included latent TB (Renflexis/Renflexis 5.5%; Remicade/Renflexis 7.4%; Remicade/Remicade 4.0%), nasopharyngitis (5.5%; 2.1%; 4.0%) and rheumatoid arthritis (3.5%; 2.1%; 4.0%). The majority of TEAEs were considered unrelated to the study drugs. TEAEs leading to study discontinuation were Renflexis/Renflexis 1.5%; Remicade/Renflexis 3.2%; Remicade/Remicade 3.0%.

The percentage of patients who had at least one SAE is as follows: Renflexis/Renflexis 3.5%; Remicade/Renflexis 6.4%; Remicade/Remicade 3.0%.

[redacted]

No deaths were reported in the transition-extension period.

Extrapolation

Health Canada granted the extrapolation of data from the manufacturer's study in rheumatoid arthritis (SB2-G31-RA) to the indications of ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, Crohn's disease, and ulcerative colitis. Health Canada stated that the scientific rationale provided by the manufacturer to support the authorization of Renflexis in each indication held by the reference biologic drug is considered adequate and is in line with Health Canada's biosimilar guidance document.

Cost and Cost-Effectiveness

The manufacturer submitted a cost comparison of Renflexis, another infliximab biosimilar (Inflectra), and reference infliximab (Remicade) for the indications reviewed. As validated by CDR, at the manufacturer submitted price of Renflexis ($525.00 per 100 mg/mL vial), the price of Renflexis is equivalent to Inflectra ($525.00 per 100 mg/mL vial) and 47% less than that of Remicade ($987.56 per 100 mg/mL vial) when using the Ontario Drug Benefit formulary.

CDR identified the following issues for consideration:

- The manufacturers of Remicade (the reference product) and Inflectra sponsor infusion centres and may also cover patient follow-up and monitoring costs. The manufacturer of Renflexis claimed that a competitive patient support program is planned for the product launch and will include nationwide infusion clinic and associated nursing support, patient reimbursement navigation, and patient financial assistance services. The comparability of patient support programs and the ease of implementing the full scope of the Renflexis patient support program are unknown at this time.
- Reimbursement criteria and the price of Remicade and Inflectra vary across CDR-participating plans. At the submitted price, in Saskatchewan, Renflexis is 46% less costly than Remicade and 19% less costly than Inflectra. Remicade is unavailable for new patients in most plans, limiting scenarios when both Remicade and Inflectra are available for the same patient.

CDEC Members:

Dr. James Silvius (Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

January 17, 2018 Meeting

Regrets:

None

Conflicts of Interest:

None