CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Final)

Infliximab SC (Remsima SC)

Indication: Rheumatoid Arthritis

Recommendation: Reimburse with Conditions

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Single Technology

What is the CADTH reimbursement recommendation for Remsima SC?

CADTH recommends that Remsima (infliximab) subcutaneous (SC) should be reimbursed by public drug plans for the treatment of rheumatoid arthritis (RA) if certain conditions are met.

What are the conditions for reimbursement?

Remsima SC should be reimbursed only if the cost does not exceed the drug plan cost of the least costly IV formulation of infliximab.

Which patients are eligible for coverage?

Remsima SC should only be covered to treat adult patients with moderately to severely active RA in a similar way to other infliximab products currently paid for.

Why did CADTH make this recommendation?

Evidence from a clinical trial demonstrated that Remsima SC is similar in efficacy to infliximab IV. At the submitted price, Remsima SC will cost more than the least costly formulation of infliximab IV currently paid for.

Key Messages

- Clinical evidence suggests that Remsima (infliximab) SC should be reimbursed to treat adults with moderately to severely active RA in a similar way to other infliximab products, only if the cost does not exceed the drug plan cost of the least expensive IV formulation of infliximab.
- Remsima SC at the submitted price (average annual costs of treatment of $17,875 to $20,779 during the induction year and $16,857 per patient in the subsequent maintenance years) would increase costs to drug plans when compared with the least expensive infliximab IV biosimilar for RA based on publicly available prices for infliximab biosimilar.

What is RA?

RA is an immune-related disease that causes pain and swelling of the joints, and it may affect other parts of the body. If untreated it can be debilitating and progress into severe disability with joint stiffness, pain, and deformity. One in every 100 Canadians has RA.

What is Remsima SC?

Remsima SC is a medication that stops the actions of a protein in the body (tumour necrosis factor alpha) and helps to decrease swelling, which slows or stops the damage from RA. Remsima SC is a new formulation (for subcutaneous administration) of Remsima IV (for intravenous administration). Remsima is similar to other products with the same chemical structure, called infliximab.

How much does Remsima SC cost?

Treatment with Remsima SC is expected to cost approximately $646.57 per 120 mg pre-filled pen or syringe, the cost of maintenance treatment with Remsima SC is $16,857 per patient per year for those with RA.

What other treatments are available for rheumatoid arthritis?

Other treatments for RA exist, including biologics and conventional disease-modifying antirheumatic drugs (e.g., methotrexate).

Unmet needs in rheumatoid arthritis

Remsima SC offers another treatment option for patients who wish to not receive their medication for RA intravenously.

How much do other treatments cost?

The annual costs associated with Remsima SC are less than Remicade IV and other branded biologic comparators (Humira, Enbrel), but more than the other available infliximab products (Inflectra, Renflexis, Avsola) and biosimilar etanercept (Brenzys, Erelzi).

INFLIXIMAB SC (REMSIMA SC — CELLTRION HEALTHCARE CANADA LTD.)

Therapeutic Area: Rheumatoid arthritis

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that infliximab subcutaneous (SC) should be reimbursed for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA), only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Infliximab SC 120 mg was noninferior to infliximab IV 3 mg/kg in one randomized, double-dummy blinded, phase I/III study (Study CT-P13 3.5; N = 357). The least squares mean change from baseline in the Disease Activity Score in 28 joints using C-reactive protein (DAS 28-CRP) improved in both the infliximab SC and infliximab IV treatment groups. The mean difference between groups was 0.27 points (95% confidence interval [CI], 0.02 to 0.52). The lower limit of the two-sided 95% CI of 0.02 was greater than the pre-specified noninferiority margin of –0.6, indicating noninferiority of infliximab SC compared with infliximab IV.

Infliximab SC at the submitted price (average annual costs of treatment of $17,875 to $20,779 during the induction year and $16,857 per patient in the subsequent maintenance years) would increase costs to drug plans when compared with the least costly infliximab IV biosimilar for RA based on publicly available prices for infliximab biosimilar ($9,640 to $10,266 per patient per maintenance year). Given infliximab SC is noninferior to infliximab IV, there is insufficient evidence to justify a cost premium over the least expensive infliximab IV biosimilar reimbursed for the treatment of moderately to severely active RA.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason
Initiation, renewal, discontinuation, and prescribing	
In a similar manner to IV formulations of infliximab.	Infliximab SC was noninferior to infliximab IV for reducing disease activity (improved DAS 28-CRP) from baseline in patients with active RA who had an inadequate response to methotrexate.
Pricing	
The drug plan cost of treatment with infliximab SC should not exceed the drug plan cost of the least costly IV formulation of infliximab.	The reviewed evidence demonstrated that infliximab SC is noninferior to infliximab IV. At the submitted price, infliximab SC would increase costs to drug plans when compared with the least costly infliximab IV biosimilar for RA based on publicly available prices.

Discussion Points

CDEC discussed the potential that a SC mode of administration may be preferred by some patients. A conclusion regarding benefit on health-related quality of life with infliximab SC treatment could not be made because the outcome measures were analyzed without comparisons in Study CT-P13 3.5.

Background

Infliximab SC has a Health Canada indication for 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 RA. It is available as a solution for SC injection in a 120 mg / mL pre-filled syringe or pre-filled pen. Patients initiating treatment with infliximab SC must receive two infliximab IV infusions as dose induction before receiving infliximab SC 120 mg once every two weeks as maintenance therapy. Patients already receiving infliximab IV maintenance therapy and who are switching to infliximab SC maintenance therapy may receive the first dose of infliximab SC 8 weeks after the last infliximab IV infusion. The product monograph indicates that the efficacy and safety of infliximab SC in patients who received infliximab IV at dosages higher than 3 mg/kg every eight weeks have not been established.

Summary of Evidence

To make their recommendation, CDEC considered the following information:

- a tailored review of one randomized, double-dummy blinded study that assessed the noninferiority of infliximab SC 120 mg biweekly versus infliximab IV 3 mg/kg every 8 weeks in adult patients with moderate to severely active RA
- patient perspectives gathered by 3 patient groups, Arthritis Consumer Experts (ACE), the Arthritis Society, and the Institute for Optimizing Health Outcomes
- one clinical specialist with expertise diagnosing and treating patients with RA
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Summary of Patient Input

Information for the submission from ACE, the Arthritis Society, and the Institute for Optimizing Health Outcomes was obtained from online surveys, and focus groups in the case of the latter organization, conducted in people with RA about how the condition affects their lives.

Patients expressed how symptoms and severity of the disease vary; RA is unique to each person who lives with it. Patients described a cycling of the disease with periods of remission or stable chronic symptoms punctuated by flares. The symptoms reported as having the greatest impact included joint pain and swelling, restricted mobility, and fatigue, which adversely affect their

daily lives, their family, and overall quality of life. Controlling the pain and swelling is key for patients, and even with treatment patients reported struggling to maintain their usual activities.

Respondents highlighted that identifying the most effective drug regimen to treat their RA required a trial-and-error approach, with many expecting that the effects of their treatments would wane with time. As well, currently available medications have troublesome or even serious side effects causing disruptions in patients' daily activities. Intolerance, especially fatigue, nausea, and infusion or injection site reactions were noted, frequently with sufficient severity to require changes in therapies. Patients expressed the need for further treatment options that could improve outcomes, acceptability, and ease of administration. The expectation of another option for SC administration of an already known drug was noted as appealing to patients.

Clinical Trials

The tailored review included one randomized, double-blind, double-dummy, noninferiority trial of patients with active RA, Study CT-P13 3.5. Eligible patients had to be 18 to 75 years with moderately to severely active RA and who had an inadequate response to at least three months of methotrexate therapy at a stable dose ranging from 12.5 to 25 mg per week. Of 357 patients enrolled, 343 received infliximab biosimilar IV 3 mg/kg at baseline and at week two as induction. Patients were then randomized (1:1) at week six to infliximab SC (120mg biweekly until week 28; N = 167) or infliximab IV (3 mg/kg every 8 weeks until week 22; N = 176). Treatments were co-administered with methotrexate orally or IV 12.5 to 25 mg per week (plus folic acid orally, at least 5 mg per week).

Outcomes

CDEC discussed the following outcomes measured in CT-P13 3.5:

- DAS 28-CRP score indicates an absolute level of disease activity with a score of 5.1 or greater being considered high disease activity, while a DAS 28 score lower than 3.2 indicates a low disease activity state and a DAS 28 score lower than 2.6 indicates remission.
- American College of Rheumatology (ACR) criteria provide a composite measure of improvement in both swollen and tender joint counts and at least 3 of 5 additional disease criteria: patient global assessment of disease activity, physician global assessment of disease activity, patient assessment of pain, Health Assessment Questionnaire (HAQ), and levels of either CRP or erythrocyte sedimentation rate. ACR 20, 50, or 70 responses represent at least a 20%, 50%, or 70% improvement, respectively.
- European League Against Rheumatism response criteria categorizes the DAS 28 response (i.e., good, moderate, or none) based on changes in DAS 28 from baseline. The higher DAS 28 improvement over time from the baseline represents better responses.
- Clinical disease activity index score ranges from 0 to 76 and the higher the score is the worse the condition is. The score can be interpreted as 0.0 to 2.8 remission, 2.9 to 10.0 low activity, 10.1 to 22.0 moderate activity, and 22.1 to 76.0 high activity.
- HAQ is a patient-centred outcome measure that asks patients to report the amount of difficulty they have in performing specific activities, and their responses are made on a scale from 0 (no difficulty) to 3 (unable to do).
- The 36-item short form health survey (SF-36) is a generic measure of health-related quality of life. All domains of the SF-36 are scored on a scale of 0 to 100, with higher scores indicating higher quality of life.

The primary end point was change from baseline in DAS 28-CRP at week 22 in Study CT-P13 3.5. Noninferiority between treatments could be declared if the lower bound of the two-sided 95% CI for the difference between groups in DAS 28-CRP at week 22 was greater than the pre-specified noninferiority margin of –0.6.

Efficacy

The least squares mean (standard error [SE]) of change from baseline in DAS 28-CRP at week 22 was 2.21 (0.221) and 1.94 (0.209) in the infliximab SC 1and infliximab IV treatment groups, respectively. The between group mean difference was 0.27 points (95% CI, 0.02 to 0.52). Noninferiority was met because the lower limit of the two-sided 95% CI of 0.02 was greater than the pre-specified noninferiority margin of –0.6.

The results for the other efficacy outcomes were similar between infliximab SC and infliximab IV.

Harms (Safety)

Adverse events were assessed up to 64 weeks of treatment. Overall adverse events occurred in 54.8% and 66.9 of patients in the infliximab SC and infliximab IV groups, respectively. Serious adverse events occurred in 3.6% of patients in the infliximab SC group and 7.4% in the infliximab IV group. Approximately 4% of patients in the infliximab SC group and 8.0% in the infliximab IV group had an adverse event leading to discontinuation.

infusion related reaction, systemic injection reaction, and delayed hypersensitivity occurred in 3.0% and 5.7% of patients in the infliximab SC and infliximab IV groups, respectively. Overall injection site reactions were reported in 17.9% of those in the infliximab SC group and 12.6% in the infliximab IV group. Approximately one-third of patients had infections (29.2% infliximab SC, 34.3% infliximab IV), primarily of the upper respiratory system. One patient in the infliximab SC group and none in the infliximab IV group developed a malignant ovarian cyst. The malignancy was possibly related to treatment by the investigator because the cyst was not detected during screening, meaning an association with study treatment could not be ruled out. During the study, the frequency of antidrug antibodies was similar in both groups.

Cost and Cost-Effectiveness

At the submitted price of $646.57 per 120 mg pre-filled pen or syringe, the cost of maintenance treatment with infliximab SC is $16,857 per patient per year for patients with RA. The first-year costs of infliximab SC depend on which infliximab IV product is chosen for the induction period, ranging from $17,875 to $20,779 per patient.

The sponsor submitted a cost comparison assessing infliximab SC compared with infliximab IV, adalimumab, certolizumab, etanercept, golimumab, and tofacitinib. The cost comparison was undertaken from the drug plan perspective and included only drug acquisition costs under the assumption that IV infusion administration costs are funded by the respective sponsors rather than public plans. The cost comparison considered both first-year costs, which includes the induction period, as well as maintenance year costs.

CADTH identified the following limitations with the sponsor's submitted cost comparison:

- the comparative efficacy of infliximab SC to non-infliximab comparators is uncertain
- the sponsor overestimated the cost of infliximab IV comparators during their first year of use.

The annual costs associated with infliximab SC ($16,857 per patient per maintenance year) are less than the branded IV infliximab product (Remicade, $19,104 per patient per maintenance year) and other branded non-infliximab biologic comparators, such as adalimumab (Humira, $20,478 per patient per year) and etanercept (Enbrel, $21,169 per patient per year), leading to cost savings in maintenance years of $340 to $4,312 per patient per year when compared with branded biologic comparators. However, infliximab SC is more expensive than the other available biosimilar infliximab products (Inflectra, Renflexis, and Avsola; $9,640 to $10,266 per patient per maintenance year) and biosimilar etanercept products (Brenzys, Erelzi; $12,566 per patient per year), leading to additional costs of $4,291 to $7,217 per patient per maintenance year when compared with other biosimilar products available for the treatment of RA.

At its submitted price, infliximab SC would be cost saving compared with branded biologic products, but would result in increased costs compared with biosimilar products. The submitted price of infliximab SC would need to be reduced by 43% for its annual cost to be equivalent to that of the least expensive biosimilar comparator, infliximab IV biosimilar.

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Sally Bean, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Allen Lefebvre, Dr. Kerry Mansell, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

March 17, 2021 Meeting

Regrets

One CDEC member did not attend.

Conflicts of Interest

One CDEC member did not participate due to considerations of a conflict of interest.

CADTH

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