CEDAC FINAL RECOMMENDATION

ROMIPLOSTIM
(Nplate – Amgen Canada Inc.)
Indication: Idiopathic Thrombocytopenic Purpura

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that romiplostim not be listed.

Reason for the Recommendation:
The Committee considered that romiplostim was not cost-effective and that the harms associated with romiplostim are uncertain. Romiplostim costs $882.50 per 250 µg vial and the manufacturer reported an incremental cost per quality-adjusted life-year of $[redacted] for romiplostim plus supportive care compared with supportive care alone, which greatly exceeds conventional standards for cost effectiveness. This confidential information was used to make the CEDAC recommendation and the manufacturer requested that this information be kept confidential pursuant to the CDR Confidentiality Guidelines.

Background:
Romiplostim has a Health Canada indication to increase the platelet levels in adult patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP):

- who are non-splenectomized and have had an inadequate response or who are intolerant to corticosteroids and/or immunoglobulins
- who are splenectomized and have had an inadequate response to splenectomy.

Romiplostim is an Fc-peptide fusion protein that increases platelet production through binding to the thrombopoietin receptor.

The Health Canada-recommended dose of romiplostim is initially 1 µg/kg weekly based on actual body weight, administered subcutaneously. The dose can be increased in 1 µg/kg increments weekly until a platelet count > 50 x 10^9/L is achieved, up to a maximum weekly dose of 10 µg/kg. Romiplostim is available as a sterile solution in 250 µg and 500 µg vials.

Summary of CEDAC Considerations:
The Committee considered the following information prepared by CDR: a systematic review of randomized controlled trials (RCTs) of romiplostim and a critique of the manufacturer's pharmacoeconomic evaluation.

Clinical Trials
The CDR systematic review included two manufacturer-sponsored, six-month, randomized, double-blind, placebo-controlled trials evaluating romiplostim. Both studies enrolled patients with chronic ITP who had an insufficient response to standard therapy and mean platelet counts ≤ 30 x 10^9/L. The two studies had identical study designs; however, one enrolled 63 patients who had undergone a splenectomy (median time since splenectomy of 6.6 years), while the other enrolled 62 patients who did not have a splenectomy. Being refractory to previous treatment was not a requirement for study enrolment, limiting the generalizability of these trials. The median number of years since ITP diagnosis was about eight in the patients with splenectomy and about two in the patients without splenectomy.

Romiplostim was administered at 1 µg/kg weekly, with dose increases based on platelet count to a maximum of 15 µg/kg weekly. In the study of splenectomized patients, 11% received a romiplostim dose ≥ 9 µg/kg weekly; it is unclear how many of these patients received greater than the Health Canada-recommended dose of 10 µg/kg weekly.

Most patients completed the six-month studies (94% of the splenectomized patients and 90% of the patients without splenectomy). Patients were followed for an additional 12 weeks or until platelets were < 50 x 10^9/L. Patients completing the studies were eligible for enrolment in a longer-term uncontrolled extension study.

Outcomes
In both studies, the primary outcome was durable platelet response, defined as ≥ six weeks with platelet counts ≥ 50 x 10^9/L during the last eight weeks of treatment and not requiring rescue medication.

The Committee discussed other outcomes that were defined a priori in the CDR systematic review protocol including the number of patients requiring rescue therapy, total number of patients who either reduced other ITP therapies by 25% or discontinued other ITP therapies, quality of life, mortality, serious adverse events, and clinically significant bleeding events.

In both studies, quality of life was assessed using the following scales: Short Form 36 (SF-36), the European Quality of Life-5 Dimensions (EQ-5D), the Patient Global Assessment, and the Immune Thrombocytopenic Purpura-Patient Assessment Questionnaire (ITP-PAQ). The ITP-PAQ is a manufacturer-developed questionnaire consisting of 10 scales assessing the impact of ITP on physical health, emotional health, work, social activity, women's reproductive health, and overall quality of life.

Clinically significant bleeding events were defined as those considered to be of grade three severity by the investigator; bleeding events were not classified by the site of bleeding. Bleeding events requiring hospitalization were not captured in the two studies.

Results

Efficacy or Effectiveness

- In both studies, the number of patients with a durable platelet response was statistically significantly higher in the romiplostim group compared with the placebo group (patients with splenectomy: 38% difference [95% CI: 23% to 53%]; patients without splenectomy: 56% difference [95% CI: 39% to 74%]).
- In the two RCTs, there were no statistically significant differences in clinically significant bleeding events between the romiplostim and placebo groups.
- In both studies, the number of patients requiring rescue therapy was statistically significantly higher in the placebo group compared with the romiplostim group.
- In patients with splenectomy, but not in patients without splenectomy, the total number of patients who either reduced or discontinued ITP therapies was statistically significantly higher in the romiplostim group compared with the placebo group, although details on the type of rescue therapies were not available.
- In both studies, no statistically significant differences in mean change scores between the romiplostim and placebo groups were observed for the total ITP-PAQ, the SF-36, the EQ-5D, and the patient global assessments scales. Statistically significant improvements for the romiplostim group relative to the placebo group were observed for some subscales of the ITP-PAQ.

Harms (Safety and Tolerability)

- One patient with prior splenectomy receiving romiplostim withdrew from the study because of increased bone marrow reticulin.
- Data were not available on the number of patients who developed more severe thrombocytopenia following discontinuation of romiplostim.
- Mortality and serious adverse events were similar between the romiplostim and placebo groups in both studies; however, the short duration of the two RCTs prevents definitive conclusions regarding long-term harms associated with romiplostim.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis of romiplostim plus supportive care (e.g., corticosteroids and/or immunoglobulins) compared with supportive care alone. They stated that the patient population being modeled were adults with chronic ITP who failed corticosteroids, intravenous immunoglobulin and Anti-D and who did not respond to, were contraindicated for, or preferred to avoid splenectomy. Key data used to inform the economic evaluation included: the two romiplostim RCTs included in the CDR systematic review, an observational study of the mortality risk associated with bleeding events in patients with ITP, and a health utility survey of Canadians without ITP. However, the two RCTs did not reflect patients who had failed corticosteroids, intravenous immunoglobulin and Anti-D; and the health utility data did not reflect the EQ-5D data collected in these RCTs. The manufacturer estimated that romiplostim plus supportive care is associated with an incremental cost per QALY of $[redacted] when compared with supportive care alone, which greatly exceeds conventional standards for cost effectiveness. The manufacturer requested that this information be kept confidential pursuant to the CDR Confidentiality Guidelines. CDR identified several key limitations with the manufacturer's analysis that could further increase the cost per QALY estimate.

At recommended doses and a price of $882.50 per 250 µg vial, patients may require one to three vials of romiplostim at a cost of $883 to $2,648 per week.

Other Discussion Points:

- Harms associated with romiplostim that are noted in the product monograph were also observed in the six-month period of the most recent Periodic Safety Update Report. Based on approximately 1,900 patients treated with romiplostim, there were 40 reports of hemorrhage events, 13 reports of hematologic malignancies, four reports of myelodysplastic syndrome, 11 cases of worsening of thrombocytopenia after discontinuing romiplostim treatment, and reports of increased bone marrow reticulin.
- The Committee discussed that bone marrow biopsies were not routinely performed in the two RCTs included in the CDR systematic review; therefore, the extent of reticulin formation in these RCTs is unknown.
- In other clinical studies of patients with ITP who were followed after romiplostim was discontinued, four of 57 patients developed thrombocytopenia of greater severity than was present before treatment.
- The Committee attempted to identify a subgroup that might benefit from romiplostim therapy. There was discussion regarding a potential unmet need for a small number of patients with symptomatic thrombocytopenia who have failed splenectomy and who are refractory or intolerant to all other treatments, as well as for bridging therapy before splenectomy; however, there is insufficient evidence on the efficacy and harms of romiplostim in these populations.
- The Committee discussed the potential benefits of reducing the use of other ITP therapies, including corticosteroids, which may result from the use of romiplostim, but considered that the potential harms associated with romiplostim are unclear and might present a greater potential risk to the patient.
- The Committee discussed the relationship between platelet counts and risk of major bleeding. In the RCTs, the inclusion criteria (platelet count < 30 x 10^9/L) and the primary outcome target platelet count (> 50 x 10^9/L) were noted to be higher than thresholds that may be used to initiate treatment in clinical practice. It was also noted that elderly patients (age > 60 years) may be at highest risk of bleeding from thrombocytopenia, and subsequent mortality, but that the mean age of patients in the included studies was 53 years.
- The Committee considered that the mechanism of action for romiplostim is not specific to ITP and may lead to off-label use in other patients with low platelet counts. Romiplostim is also being evaluated for myelodysplastic syndrome, advanced malignancy on chemotherapy, non-Hodgkin lymphoma, and children with ITP.
- There are currently active clinical trials evaluating romiplostim for myelodysplastic syndrome. However, in one country, these trials have been halted pending investigation of a potential risk of progression or transformation to acute myelogenous leukemia associated with romiplostim.

CEDAC Members Participating:

March 24: Dr. Robert Peterson (Chair), Dr. Anne Holbrook (Vice-Chair), Dr. Michael Allan, Dr. Ken Bassett, Dr. Bruce Carleton, Dr. Doug Coyle, Mr. John Deven, Dr. Alan Forster, Dr. Laurie Mallery, Mr. Brad Neubauer, Dr. Lindsay Nicolle, Dr. Yvonne Shevchuk, and Dr. Kelly Zarnke.

May 19: Dr. Robert Peterson (Chair), Dr. Michael Allan, Dr. Bruce Carleton, Dr. Doug Coyle, Mr. John Deven, Dr. Alan Forster, Dr. Laurie Mallery, Mr. Brad Neubauer, Dr. Lindsay Nicolle, Dr. Yvonne Shevchuk, and Dr. Kelly Zarnke.

Regrets:
March 24: None

May 19: Dr. Anne Holbrook (Vice-Chair) and Dr. Ken Bassett.

Conflicts of Interest:
One CEDAC member reported a conflict of interest and did not participate in the vote.

About this Document:
CEDAC provides formulary listing recommendations to publicly funded drug plans. Both a technical recommendation and plain language version of the recommendation are posted on the CADTH website when available.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CEDAC made its recommendation.

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

The Final CEDAC Recommendation 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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