CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

BUROSUMAB (CRYSVITA — KYOWA KIRIN LIMITED)
Indication: Treatment of X-linked hypophosphatemia.

RECOMMENDATION
The CADTH Canadian Drug Expert Committee recommends that burosumab be reimbursed for the treatment of X-linked hypophosphatemia (XLH) only if the following conditions are met.

Conditions for Reimbursement

Initiation Criteria
1. Treatment can be initiated in pediatric patients who are at least one year of age and in whom epiphyseal closure has not yet occurred, who have:
   - 1.1. a clinical presentation consistent with XLH, including:
     - 1.1.1. fasting hypophosphatemia, and
     - 1.1.2. normal renal function (defined as fasting serum creatinine below the age-adjusted upper limit of normal), and
   - 1.2. radiographic evidence of rickets with a rickets severity score (RSS) total score of two or greater, and
   - 1.3. a confirmed phosphate-regulating endopeptidase homolog, X-linked (PHEX) gene variant in either the patient or in a directly related family member with appropriate X-linked inheritance.

Renewal Criteria
1. Patients should be assessed on an annual basis. Treatment with burosumab can be renewed as long as the patient does not meet any of the following discontinuation criteria.

Discontinuation Criteria
1. In pediatric patients in whom epiphyseal closure has not yet occurred, reimbursement of treatment with burosumab should be discontinued if:
   - 1.1. the 12-month RSS total score has not improved from baseline, when baseline represents the initiation of treatment, or
   - 1.2. the RSS total score achieved after the first 12 months of therapy has not been maintained subsequently.
2. In adolescent or adult patients who initiated burosumab based on the aforementioned criteria for pediatric patients, burosumab should be discontinued if any of the following occur: hyperparathyroidism, nephrocalcinosis, or evidence of fracture or pseudofracture based on radiographic assessment.

Prescribing Conditions
1. Burosumab should only be prescribed by a physician working in a comprehensive team of health care providers who are experienced in the diagnosis and management of XLH.

Pricing Conditions
1. Price reduction.

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Reasons for the Recommendation

1. In one randomized, open-label, phase III trial (Study CL301, N = 61) that compared the efficacy and safety of burosumab with active control (oral phosphate and active vitamin D therapy) in pediatric patients (one year old to 12 years of age) with XLH and an RSS total score of two or more, burosumab every two weeks showed improvements in radiographic end points (as measured by RSS and Radiographic Global Impression of Change [RGI-C] scale scores), improved serum phosphorus concentration, and reduced lower extremity deformities.

2. One randomized, double-blind, placebo-controlled, phase III trial (Study CL303, N = 134) evaluated the efficacy and safety of burosumab in adult patients (18 to 65 years old) with XLH. Compared with placebo, burosumab was associated with statistically significant improvements in serum phosphorus concentration and patient-reported stiffness at week 24; however, the comparative benefit of burosumab in adults with XLH is difficult to determine given that it has not been compared with standard of care (oral phosphate supplements and active vitamin D analogues), which was withheld in the placebo comparator group of Study CL303. In addition, burosumab did not show statistically significant improvements in measures of pain, physical function, and fatigue when compared with placebo. The proportion of patients who had full healing of active fracture or pseudofracture

was measured at week 24; however, the clinical significance of these results is limited as the presence of pseudofractures and fractures appeared to have no relationship with pain scores at baseline, and no statistical test comparing the two treatment groups was conducted.

3. CDEC acknowledged that there is an unmet need for the treatment of XLH and that burosumab is the first Health Canada–approved treatment to target the underlying pathophysiology of excess FGF23 in XLH.
4. CADTH Common Drug Review reanalysis of a cost-utility model submitted by the sponsor found that burosumab was unlikely to be cost-effective at the submitted price, with an incremental cost-effectiveness ratio (ICER) of $2.7 million per quality-adjusted life-year (QALY) in pediatric patients. Results for adult patients were uncertain due to a lack of appropriate clinical data but were estimated at $3.7 million per QALY gained. A 93% price reduction is required for burosumab to achieve an ICER of $50,000 per QALY gained in the pediatric population based on the CADTH best estimate.

Implementation Considerations

- The sponsor should cover the cost of the PHEX mutation testing required to support the diagnosis of XLH.

Discussion Points

- The committee discussed that the benefit of burosumab in adults is uncertain. The included studies provide little evidence of the benefit of burosumab in patients diagnosed as adults. In adults who were diagnosed as children (which seems to be consistent with the patient population included in Study CL303), evidence of comparative efficacy is lacking given that burosumab was not compared with conventional therapy (oral phosphate supplements and active vitamin D analogues).
- Despite long-term extension studies with results up to week 160, there is uncertainty regarding the long-term efficacy and safety of burosumab, which is of particular concern given that clinical experts suggested that patients would likely be treated with lifelong burosumab. It is unclear what role intermittent dosing could play in the management of patients with XLH.
- The committee noted that there may be a harms signal with respect to tooth abscess events in patients receiving burosumab in Study CL301, where tooth abscesses were reported by 28% of those in the burosumab group versus 9% of those in the oral phosphate and active vitamin D treatment group.
- The committee discussed that the evidence for benefit of burosumab is likely achieved in children and before epiphyseal plates have fused, which would be expected to occur in early adolescence. Furthermore, the committee noted that there is a lack of evidence for the use of burosumab in people between 13 and 17 years of age, as the cut-off age in Study CL301 was 12 years old in order to ensure that patients enrolled had open epiphysis for the duration of the study.
- The committee discussed that, at the discretion of the treating physician, a closely monitored discontinuation of therapy should be considered in adolescents who have completed growth (epiphyseal closures confirmed by radiological examination).
- The committee discussed that a national patient registry to track the progress of Canadian patients with XLH would be beneficial in collecting additional real-world evidence in this patient population.
- The committee discussed the potential for uncertainty in diagnosis and characterization of disease severity based on an observed PHEX gene variant. Given the rarity of the disease and the large number of pathogenic variants in the PHEX gene, it is difficult to determine specific genotype-phenotype relationships.

Background

Burosumab has a Health Canada indication for the treatment of XLH in adult and pediatric patients one year of age and older. Burosumab is a recombinant human immunoglobulin G subclass 1 monoclonal antibody that binds to the N-terminal domain of FGF23. The Health Canada–recommended starting dose of burosumab in pediatric patients with XLH (one year old to younger than 18 years old) is 0.8 mg/kg of body weight, rounded to the nearest 10 mg, administered by subcutaneous (SC) injection every two weeks. The Health Canada–recommended starting dose of burosumab in adult patients with XLH (18 years of age and older) is 1 mg/kg of body weight, rounded to the nearest 10 mg up to a maximum dose of 90 mg, administered by subcutaneous (SC) injection every four weeks. In both pediatric patients and adults, the dose of burosumab may be adjusted based on serum phosphorus levels, with a maximum dose of 90 mg. Burosumab should be administered by a health professional.

Summary of Evidence Considered by CDEC

The committee considered the following information prepared by the CADTH Common Drug Review: a systematic review of pivotal and protocol-selected studies of burosumab and a critique of the manufacturer's pharmacoeconomic evaluation. The committee also considered input from clinical experts with experience in treating patients with XLH, and patient group–submitted information about outcomes and issues important to patients.

Summary of Patient Input

One patient group, the Canadian Organization for Rare Disorders (CORD) with support of the XLH Network, provided input for this submission. Patient perspectives were obtained from an online survey as well as individual interviews with patients and parents who had experience with burosumab. The following is a summary of key input from the perspective of the patient group.

- Patients indicated that the symptoms of XLH include chronic debilitating pain, bone and joint deformities in the legs and the spine, severe dental problems, fractures and stiffness, short stature, hearing problems, and osteoarthritis with aging.
- Current treatments (surgeries and medication regimens [with multiple administration per day and side effects]) for XLH added to the burden of disease symptoms and were associated with significant social, educational, or work challenges; financial difficulties; and psychological impacts on patients and their families.
- Patients indicated that existing therapies (prior to burosumab) had only, at best, moderate benefit with regards to addressing symptoms or reducing disease progression, with many feeling the impact was limited or very limited.
- For adults, the physical symptoms (bone and joint damage) and psychological impacts of XLH accumulate over time and have a serious deleterious impact on the quality of life for the patients and their families.
- Patients expect that new treatments would reduce or eliminate the symptoms of XLH, including pain, bowed legs, fractures, and fatigue, and most importantly, stop disease progression.

Clinical Trials

The systematic review included four studies, three in children (CL301, CL201, and CL205) and one in adults (CL303) described as follows:

- Study CL301 (N = 61) was a multi-centre, randomized, open-label, phase III study comparing the efficacy and safety of burosumab with active control (oral phosphate and active vitamin D therapy) in children (one to 12 years of age) with XLH. Eligible patients were randomized in a 1:1 ratio to receive either open-label burosumab (administered by SC injection) every two weeks or phosphate and active vitamin D therapy (administered orally) daily for a total of 64 weeks. Patients randomized to the burosumab treatment group received burosumab at a starting dose of 0.8 mg/kg every two weeks, which could be titrated to 1.2 mg/kg every two weeks based on fasting serum phosphorus concentrations. The maximum allowable dose of burosumab per administration was 90 mg. For patients randomized to the active control treatment group, the dose of oral phosphate and active vitamin D therapy was administered on an individualized basis at the discretion of the investigator. Calcitriol and alfacalcidol dosages were adjusted based on the clinical and laboratory values that guide best possible treatment.
- Study CL201 (N = 52) was a randomized, multi-centre, open-label, dose-finding, phase II study to assess the efficacy and safety of burosumab in children (five to 12 years old) with XLH. Patients were randomized 1:1 to every two weeks or every four weeks burosumab via SC injection for a total of 64 weeks followed by a long-term extension phase during which patients in the every four weeks group shifted to receive burosumab every two weeks at 60% of the dose administered every four weeks (rounded to the nearest 10 mg). In patients randomized to burosumab every two weeks, the initial doses of burosumab were 0.1 mg/kg, 0.2 mg/kg, or 0.3 mg/kg every two weeks, subsequently adjusted every four weeks in 0.3 mg/kg increments, as needed, based on two-week post-dose (peak) fasting serum phosphorus levels.
- Study CL205 (N = 13) was a multi-centre, open-label, single-arm, phase II study in children (one to four years old) with XLH who were treatment-naive or had previously received standard therapy with oral phosphate and active vitamin D. The CL205 study assessed the safety and efficacy of burosumab administered via SC injections every two weeks for a total of 64 weeks. Patients who were receiving oral phosphate and active vitamin D therapy discontinued treatment during screening and for the duration of the study. All patients received burosumab at a starting dose of 0.8 mg/kg every two

weeks, which could be titrated to 1.2 mg/kg every two weeks at any time during the study if a patient met the dose-adjustment criteria. Results were only available until week 40.

- Study CL303 (N = 134) was a randomized, double-blind, placebo-controlled, multi-centre, phase III study that evaluated the efficacy and safety of burosumab in adults (18 to 65 years old) with XLH. Patients were randomized in a 1:1 ratio to receive burosumab or placebo every four weeks for a total of 24 weeks followed by a long-term extension phase during which patients in the placebo group shifted to receive burosumab at the same dosage as in the active treatment group. Patients randomized to the burosumab treatment group received burosumab 1 mg/kg (rounded to the nearest 10 mg) with a maximum allowable dose of 90 mg.

There were a number of limitations noted for these studies. First, the CL301, CL201, and CL205 studies were open-label studies, meaning patients were aware of the treatment allocation; therefore, bias may be introduced in the evaluation of patient-reported outcomes (such as the scales measuring pain, fatigue, or health-related quality of life), particularly for the within-group comparison with baseline (studies CL201 and CL205). In contrast, assessments of RSS and RGI-C were conducted by radiologists who were blinded to patient identity, treatment status of the patient, and the timing of the radiographs, which would have limited investigator bias for these two outcomes.

Second, with the exception of Study CL303, which included the change from baseline to week 24 in Brief Pain Inventory (BPI) worst pain score, Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index stiffness score, and WOMAC physical function score in its adjustment for multiple testing, there was no control for multiplicity among the other secondary outcomes analyzed from Study CL303 or any of the secondary outcomes in studies CL301, CL201, and CL205. Hence, the results of these end points should be interpreted with consideration of the potential for inflated type I error.

Patients in the placebo group of Study CL303 did not receive any active or supportive treatment; however, in clinical practice symptomatic patients would likely receive conventional therapy of oral phosphate supplements and active vitamin D analogues. Hence, the CL303 study was biased in favour of the burosumab treatment group, especially for the primary outcome (proportion of patients achieving mean serum phosphorus levels above the lower limit of normal) given that patients in the placebo treatment group did not receive oral phosphate supplements, and patients had to have serum phosphorus levels lower than the lower limit of normal (0.81 mmol/L) in order to be eligible to enrol in the study. Thus, the findings of Study CL303 may not reflect the comparative effectiveness to be achieved in the real-world setting.

Outcomes

Outcomes were defined a priori in the CADTH Common Drug Review systematic review protocol. Of these, the committee discussed the following:

- RSS — A 10-point scale (four points for the wrists and six points for the knees) used to evaluate the severity of rickets. Assessment of the wrists and knees is based on the degree of metaphyseal fraying, concavity, and the proportion of growth plate affected. A score of 10 represents severe rickets, while a score of zero indicates an absence of metaphyseal cupping and fraying.
- RGI-C — A scale that measures the change in the severity of rickets. The RGI-C is a seven-point change scale that provides an assessment of the change in bone structure associated with the pathophysiology of hypophosphatasia. A score of zero represents no change, whereas a reduction of three points represents severe worsening, and an increase of three points indicates complete healing of the skeletal disease.
- BPI — A questionnaire designed to provide information on pain intensity (the sensory dimension, four items) and the degree to which pain interferes with functioning in daily living (seven life domains). The scores for the two BPI subscales (pain intensity and pain interference) range from zero to 10 and are calculated using the mean of their corresponding items' scores. The total score of BPI is the mean of the two subscale scores. A high score represents a high pain intensity or pain interference.
- The Brief Fatigue Inventory — A self-reported questionnaire to assess the severity of fatigue and the impact of fatigue on daily functioning. Two dimensions are measured: severity of fatigue and the interference of fatigue on daily life. The items are measured on a zero to 10 numeric rating scales. For the dimension of severity of fatigue, zero represents "no fatigue" and 10 represents "fatigue as bad as you can imagine." For the dimension of interference from fatigue, zero represents "does not interfere" and 10 represents "completely interferes."

- WOMAC — A self-administered questionnaire assessing pain, stiffness, and physical functioning in patients with hip and knee osteoarthritis. Higher scores on the WOMAC indicate worse pain, stiffness, and functional limitations.
- The Faces Pain Scale – Revised — A self-reported measure for evaluating pain intensity in children. It consists of a series of horizontal gender-neutral faces that depict a neutral facial expression of "no pain" at the left to "most pain possible" expression at the right. The Faces Pain Scale – Revised has six faces scoring from zero to 10. The patients are instructed to point to the face that shows how much they hurt. Higher scores indicate more severe pain.
- The six-minute walk test (6MWT) — A test that measures the distance a patient can walk on a hard, flat surface over a six-minute period.
- Patient-Reported Outcomes Measurement Information System scores for pediatric pain interference, fatigue, and physical function mobility scales — is a set of measures covering different domains of physical, mental and social health.
- Serum phosphorus.
- Fractures and pseudofractures.

The primary outcome in Study CL301 was change from baseline in rickets at week 40 as assessed by the RGI-C global score. The primary outcome in Study CL201 was the change from baseline in severity of rickets as measured by RSS total score. The primary outcome in Study CL205 was change from baseline in serum phosphorus at week 40. The primary outcome in Study CL303 was the proportion of patients achieving mean serum phosphorus levels above the lower limit of normal.

Efficacy

Pediatric Patients

RSS Total Score

- In Study CL301, the LS (least squares) mean difference in RSS total score for the difference between the burosumab group and the active control group in change from baseline at week 40 was −1.34 (95% confidence interval [CI], −1.74 to −0.94; *P* < 0.0001) and at week 64 it was −1.21 (95% CI, −1.59 to −0.83; *P* < 0.0001) in favour of burosumab.
- In Study CL201, (primary end point) and Study CL205, pediatric patients who received burosumab every two weeks showed consistent improvements as demonstrated by within-group change from baseline to week 40 in RSS total score (−1.06 [95% CI, −1.28 to −0.85; *P* < 0.0001] in Study CL201, and −1.73 [95% CI, −2.03 to −1.44; *P* < 0.0001] in the Study CL205).

Radiographic Global Impression of Change

- In Study CL301, (primary end point), the LS mean RGI-C global score at week 40 was 1.92 in the burosumab group and 0.77 in the active control group, a statistically significant difference of 1.14 (95% CI, 0.83 to 1.45; *P* < 0.0001); this improvement was maintained at week 64 (1.02 [95% CI, 0.72 to 1.33; *P* < 0.0001]).
- In Study CL201, RGI-C global score improved by 1.66 (95% CI, 1.48 to 1.84; *P* < 0.0001) at week 40, and at week 64 was improved by 1.56 (95% CI, 1.34 to 1.78; *P* < 0.0001) in the burosumab every two weeks treatment group.
- In Study CL205, RGI-C global score improved by 2.33 (95% CI, 2.16 to 2.51; *P* < 0.0001) in the burosumab every two weeks treatment group.

Serum Phosphorus Levels

- Study CL301:
  - The difference in serum phosphorus between the burosumab group and the active control group in change from baseline at week 40 was 0.25 mmol/L (95% CI, 0.20 to 0.30; *P* < 0.0001) in favour of burosumab, and at week 64 it was 0.24 mmol/L (95% CI, 0.19 to 0.29; *P* < 0.0001) in favour of burosumab.
  - Of the 29 patients randomized to the burosumab treatment group, 17 patients (58.6%) and 19 patients (65.5%) had a serum phosphorus concentration within the normal range (1.03 mmol/L to 1.97 mmol/L) at week 40 and at week 64, respectively. Of the 32 patients randomized to the active control group (oral phosphate and active vitamin D therapy), only one patient (3.1%) had a serum phosphorus concentration within the normal range (1.03 mmol/L to 1.97 mmol/L) at week 40 and at week 64.
- In Study CL201, the mean (standard deviation) serum phosphorus levels increased in the burosumab every two weeks treatment group from 0.77 (0.131) mmol/L at baseline to 1.07 (0.128) mmol/L at week 40, and to 1.08 (0.144) mmol/L at week 64. At week 40, 17 out of 26 patients (65.4%), and at week 64, 16 out of 24 patients (66.7%) had a serum phosphorus level within the normal range (1.03 mmol/L to 1.97 mmol/L).

- In Study CL205 (primary end point), mean (standard deviation) serum phosphorus levels increased with burosumab to 1.12 (0.158) mmol/L at week 40. At week 40, 10 patients (76.9%%) had a serum phosphorus level within the normal range (1.03 mmol/L to 1.97 mmol/L).

Other Outcomes

- 6MWT
  - In Study CL301, the difference in 6MWT distance walked between the treatment groups for the change from baseline to week 40 was 43 metres (95% CI, −0.3 to 87; *P* = 0.0514), which was not statistically significant different, and at week 64 it was 46 metres (95% CI, 2 to 89; *P* = 0.0399) in favour of burosumab.
  - In Study CL201, LS mean (95% CI) for the change from baseline in 6MWT distance walked at week 64 was 52.67 metres (95% CI, 35.39 to 69.95; *P* < 0.0001) in the burosumab every two weeks treatment group.
- No improvements in pain, fatigue, and physical function were demonstrated.

Adult Patients (Study CL303)

- Serum Phosphate (primary end point): a statistically significantly higher percentage of patients in the burosumab group achieved a phosphorus concentration above the lower limit of normal (0.81 mmol/L) across the midpoints of the dose intervals through week 24 compared with placebo (94.1% versus 7.6%, *P* < 0.0001).
- BPI worst pain scores were not significantly different between burosumab and placebo at week 24. BPI pain severity scores and BPI pain interference scores were also not significantly different between burosumab and placebo at week 24.
- WOMAC physical function impairment score at week 24 was not statistically different between the burosumab or placebo groups after multiplicity adjustment.
- WOMAC stiffness score LS mean [95%] difference between treatment groups at week 24 was −8.31 (95% CI, −14.68 to −1.94; *P* = 0.0106). While statistically significant in favour of burosumab, there is no minimal clinically important difference established for this scale.
- Fatigue, as measured by the Brief Fatigue Inventory, did not demonstrate a statistically significant reduction with burosumab at 24 weeks.
- The difference in the 6MWT between treatment groups for the change from baseline to week 24 was 19.93 metres (95% CI, 4 to 36; *P* = 0.0120) in favour of burosumab. This difference does not exceed the minimal clinically important difference for patients with hypophosphatasia of 31 metres. This end point was exploratory.
- Numerically more patients experienced healing of fractures and pseudofractures (both exploratory outcomes) with burosumab compared with placebo at week 24. At week 24, 50% (16 out of 32) patients in the burosumab group had full healing of at least one active fracture or pseudofracture as compared with 13% (5 out of 38) patients in the placebo group. The correlation between fracture healing and pain relief has not been established.

Harms (Safety)

- All patients receiving burosumab in the CL301, CL201, and CL205 trials experienced at least one treatment-emergent Adverse event (TEAE). In Study CL301 84% (27 out of 32) of the patients in the active control group experienced at least one TEAE.
- In Study CL303, 94.1% of patients in the burosumab group and 92.4% in the placebo group experienced at least one TEAE.
- In Study CL301, serious adverse events (SAEs) were reported for three patients (10%) in the burosumab group and three (9%) in the active control group. In Study CL201, no patient in the burosumab every two weeks treatment group experienced an SAE. In Study CL205, one patient in the burosumab every two weeks treatment group experienced an SAE. In Study CL303, SAEs were reported for two patients (2.9%) in the burosumab group and two patients (3%) in the placebo group.
- No patient withdrew from treatment or from the trials for adverse events and no deaths were reported during the trials.
- In Study CL301, fifteen patients in the burosumab group (52%) experienced injection site reactions. Hypersensitivity TEAEs were experienced by 11 patients (38%) in the burosumab group and six patients (19%) in the active control group. Tooth abscesses were experienced by eight patients (28%) in the burosumab group and three patients (9%) in the active control

group. No TEAEs of hyperphosphatemia, ectopic mineralization, or restless leg syndrome were reported in either treatment group.

- In Study CL303, eight patients (11.8%) in the burosumab group and eight patients (12.1%) in the placebo group experienced TEAEs of injection site reactions. Hypersensitivity were reported for four patients (burosumab: 5.9%; placebo: 6.1%) in each treatment group. TEAEs of hyperphosphatemia were reported for four (5.9%) patients in the burosumab group and no patients in the placebo group. A total of eight (11.8%) patients in the burosumab group and five (7.6%) patients in the placebo group had a TEAE of restless leg syndrome or limb discomfort (13.5). Tooth abscesses were experienced by nine patients (13.2%) in the burosumab group and five patients (7.6%) in the placebo group. No TEAEs of ectopic mineralization were reported in either treatment group during the double-blind period.

Cost and Cost-Effectiveness

Burosumab is available as single-use vials of 10 mg/mL, 20 mg/mL, and 30 mg/mL for SC administration. The recommended starting dose regimen for pediatric patients is 0.8 mg/kg of body weight, rounded to the nearest 10 mg, administered every two weeks. The recommended dose regimen in adults is 1 mg/kg of body weight, rounded to the nearest 10 mg, administered every four weeks. Dose adjustment is based on fasting serum phosphorus levels. At the sponsor's submitted price of $4,992.29 per 10 mg/mL, the annual cost of burosumab may range from $129,780 to $1,168,196 per pediatric patient and $454,298 to $584,098 per adult patient.

The sponsor submitted a cost-utility analysis comparing burosumab with best supportive care (BSC) in patients (pediatric and adult) with XLH from the perspective of the Canadian health care payer over a lifetime time horizon. Two subgroups of interest were considered in the economic evaluation, defined by the patient's baseline age: pediatric (one to 17 years old) and adult (18 years of age and older) populations. BSC was defined differently by age: in the pediatric population, BSC consisted of phosphate and vitamin D; in adults, BSC consisted of phosphate, vitamin D, and/or calcimimetic. The pediatric model consisted of three health states: high total RSS (1.5 or greater); low total RSS (lower than 1.5); and death. At the age of 18, all alive patients from the pediatric model were transitioned to the adult model by entering the "alive without fracture" health state. The adult model was based on three health states: alive without fractures; alive with fractures; and death. Relative treatment effects were based on the trial data from studies CL201, CL205, and CL301 for the pediatric model, and CL303 for the adult model. Patients in the "alive with fractures" health state had an increased mortality risk after the age of 50, with Canadian general population mortality considered for the other health state. Patients were assumed to receive burosumab until age 18; thereafter, a fixed proportion of patients were assumed to discontinue burosumab based on the rate observed in the CL303 trial, applied throughout the entire lifetime of the model. Drug costs were based on the sponsor's submitted price or the Ontario Drug Benefit Formulary and included the cost of drug administration. Within the same health state, utilities and costs were assumed to differ by treatment. In the sponsor's base case, the ICER of burosumab was $1,364,863 and $1,119,456 per QALY gained compared with BSC in the pediatric and adult subgroups, respectively.

CADTH identified the following key limitations with the sponsor's submitted economic analysis:

- The comparative clinical data informing the model are not robust. In the pediatric model, this involved pooling single-arm and clinical registry studies with an active control randomized trial (Study 301). In the adult model, the BSC group was informed by the placebo group of Study 303 in which patients received no active treatment.
- Long-term efficacy is uncertain as the relative benefit of burosumab observed in short-term trials were extrapolated over a lifetime time horizon.
- The direct clinical relevance of radiologically based outcome measures are unclear in the pediatric model. It is uncertain whether a total RSS cut-off of 1.5 would reflect meaningful differences in disease health states. Furthermore, the adult phase of the model was based on fractures, which was an exploratory outcome in Study 303 that was examined post hoc.
- According to clinical experts consulted by CADTH, long-term assumption of treatment discontinuation was considered implausible in the adult phases of the model.
- Treatment-specific health state utility and costs values were applied with higher utility values and lower costs assigned to patients on burosumab for otherwise identical health states.
- Increased risk of death was assumed for patients experiencing fracture after age 50 based on data from an observational study from the UK. No deaths were reported in the trial and it remains speculative whether interventions that reduce fractures would impact mortality in this patient population.

CADTH undertook a reanalysis that assumed identical utility values by health state, applied no discontinuation after the initial 12 months of treatment, and used Canadian estimates for fracture-related mortality. The CADTH reanalyses were aligned with the sponsor's findings that burosumab is not cost-effective for either the pediatric or the adult subgroup. CADTH, however, reported much

higher ICER estimates than the sponsor: $2.7 million per QALY in pediatric populations and more than $3.7 million per QALY in adult populations when compared with BSC. Price reductions of 93% to 94% would be required for the ICER of burosumab to fall below $50,000 per QALY when compared with BSC. CADTH was unable to address the uncertainty with the clinical data given the paucity of literature establishing differences in clinically important outcomes and the lack of long-term data.

December 11, 2019 Meeting (Initial)

CDEC Members

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

Regrets

One CDEC member did not attend.

Conflicts of Interest

None.

May 20, 2020 Meeting (Reconsideration)

CDEC Members

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

Regrets

None.

Conflicts of Interest

None.