CEDAC FINAL RECOMMENDATION and REASONS for RECOMMENDATION

USTEKINUMAB
(Stelara™ – Janssen-Ortho Inc.)
Indication: Chronic Moderate to Severe Plaque Psoriasis

Description:
Ustekinumab is a human monoclonal antibody that binds to interleukins 12 and 23. It is approved by Health Canada for the treatment of adult patients with chronic moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. The recommended dose is 45 mg administered at weeks zero, four, and then every 12 weeks thereafter. Alternatively, ustekinumab 90 mg may be used in patients weighing more than 100 kg.

Dosage Forms:
Supplied as ustekinumab 45 mg in 0.5 mL solution for subcutaneous injection.

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that ustekinumab be listed for patients with severe, debilitating psoriasis who meet all of the following criteria:

1. Body surface area (BSA) involvement of >10% and/or significant involvement of the face, hands, feet or genital region;
2. Failure to respond to, contraindications to, or intolerant to methotrexate and cyclosporine;
3. Failure to respond to, intolerant to, or unable to access phototherapy.

Ustekinumab 45 mg should initially be given at weeks 0, 4 and 16. Response must be assessed prior to a fourth dose and further doses provided only for responders. Potential criteria for defining response are achievement of a ≥75% reduction in Psoriasis Area Severity Index (PASI) score, or a ≥ 50% reduction in PASI with a ≥ 5 point improvement in the Dermatology Life Quality Index (DLQI) or a significant reduction in BSA involved, considering important regions such as the face, hands, feet or genital region.

Reasons for the Recommendation:
1. In two double-blind randomized controlled trials, ustekinumab achieved statistically significantly higher PASI 75 and PASI 100 response rates and improved measures of quality of life compared with placebo. In a third randomized controlled trial, ustekinumab achieved statistically significantly higher PASI 75 and PASI 100 response rates compared with etanercept.

2. In two randomized controlled trials, patients were assessed after a third dose and all non-responders were discontinued prior to receiving a fourth dose. There are no data from trials on how non-responders after a third dose respond to a fourth dose.

3. At the recommended maintenance dose of 45 mg every 12 weeks, the annual cost of ustekinumab is similar to adalimumab and etanercept.

Summary of Committee Considerations:

The Committee considered the results of a systematic review that included three randomized controlled trials (RCTs) (N=2899) evaluating the effects of ustekinumab in patients with chronic moderate to severe plaque psoriasis. Two double-blind RCTs, PHOENIX 1 and PHOENIX 2, compared ustekinumab 45 mg and 90 mg with placebo and one open-label assessor-blinded RCT, ACCEPT, compared ustekinumab 45 mg and 90 mg with etanercept 50 mg. Ustekinumab was given at weeks 0, 4 and every 12 weeks; etanercept was given twice weekly.

All three trials reported the primary outcome of patients achieving a ≥75% reduction in the Psoriasis Area and Severity Index (PASI) score at 12 weeks. In the PHOENIX trials, response to three doses of ustekinumab was assessed at 28 weeks and treatment was discontinued in non-responders. Other outcomes included PASI 100, physician global assessment scores and quality of life.

In all three trials, there were patients who had previously received biologics for psoriasis (50% in PHOENIX 1, 40% in PHOENIX 2, 20-25% in ACCEPT). Approximately 50 to 60% of patients enrolled in the PHOENIX trials and all patients enrolled in the ACCEPT trial had an inadequate response, intolerance or a contraindication to at least one conventional systemic therapy (methotrexate, cyclosporine or psoralen plus ultraviolet A light).

The number needed to treat (NNT) to achieve a PASI 75 response after 12 weeks was approximately 2 in the PHOENIX trials for both doses of ustekinumab, compared with placebo and, in the ACCEPT trial compared with etanercept, the NNT was 10 for ustekinumab 45 mg and 6 for ustekinumab 90 mg. Significantly more patients receiving ustekinumab achieved PASI 100 or achieved a physician global assessment score of cleared or minimal compared with placebo and etanercept. Improvements in the Dermatology Life Quality Index scores were statistically and clinically significant for the ustekinumab 45 mg and 90 mg groups compared with placebo in both PHOENIX 1 and PHOENIX 2.

Based on the randomized withdrawal of ustekinumab in PHOENIX 1 from weeks 40 to 76, patients achieving PASI 75 at week 40 and continuing ustekinumab were significantly more likely to maintain a PASI 75 response compared with patients withdrawn from ustekinumab and the difference was statistically significant.

After 12 weeks, rates of serious adverse events and withdrawals due to adverse events were similar for ustekinumab, etanercept and placebo groups. The durations of placebo- or etanercept-controlled phases of the trials were too short to assess the long-term comparative harm of ustekinumab. Serious adverse events reported up to 52 and 76 weeks in the PHOENIX trials were predominantly infections, cardiac disorders, malignancies and nervous system disorders.

The manufacturer submitted a cost utility analysis comparing ustekinumab (45 mg every 12 weeks) to etanercept (50 mg weekly) based on the results of the ACCEPT trial where the clinical benefits at 12 weeks were extrapolated over a 10-year time horizon. The manufacturer found ustekinumab was less costly (by 14%) when compared to etanercept. Further, they reported a marginal increase in QALYs for ustekinumab (3%) when compared to etanercept, although the clinical importance of this gain is unclear.

The manufacturer has requested that specific results of the ustekinumab pharmacoeconomic analysis remain confidential pursuant to the Confidentiality Guidelines of the Common Drug Review. Results are robust to assumptions regarding baseline quality of life, dropout rates, and hospitalization rates. Use of higher doses (such as 90 mg) or increased frequency of use (every 8 weeks) will lead to greater costs for ustekinumab compared to etanercept (50 mg weekly).

At the price of $4,200 per vial, at 6 doses per year, in the first year, the annual cost of ustekinumab is $25,200; cost of treatment in subsequent years ranges from $16,800 to $21,000 (for 4 to 5 doses per year), which is similar to etanercept ($25,134 first year, $20,421 thereafter) and adalimumab ($18,574 first year, $17,887 thereafter), less expensive compared to infliximab ($40,740 first year, $25,220 thereafter), and more expensive compared to alefacept after the first year ($29,976 first year, $14,988 thereafter).

Of Note:

1. Both published and unpublished data were reviewed and taken into consideration in making this recommendation.
2. In all three trials, the response to ustekinumab 45 mg or 90 mg was similar. In the randomized dose intensification phase of PHOENIX 2 from weeks 28 to 52, PASI responses were similar among all re-randomized ustekinumab patients on the every 8 week dosing regimen compared with the every 12 week dosing regimen (35% versus 32%). The Committee felt there was insufficient evidence at this time to support increased dose and frequency of administration of ustekinumab based on its assessment of cost-effectiveness.
3. The Committee had concerns about the lack of long-term controlled data on harms associated with a biologic with a novel mechanism of action. There is a need for careful consideration of the balance of possible benefits and harms, particularly given the potential risks of developing infections and malignancies associated with biologics that modulate immune function.
4. Given the high cost of biologic agents, expansion of phototherapy access into geographical areas where it is currently unavailable should be considered.
5. This document has been edited to remove confidential information at the manufacturer's request in conformity with the CDR Confidentiality Guidelines.

Background:

CEDAC provides formulary listing recommendations to publicly funded drug plans. Recommendations are based on an evidence-based review of the medication's effectiveness and safety and an assessment of its cost-effectiveness in comparison to other available treatment options. For example, if a new medication is more expensive than other treatments, the Committee considers whether any advantages of the new medication justify the higher price. If the recommendation is not to list a drug, the Committee has concerns regarding the balance between benefit and harm for the medication, and/or concerns about whether the medication provides good value for public drug plans.