# CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

## ADALIMUMAB
## (Humira – AbbVie Corporation)
## New Indication: Hidradenitis Suppurativa

### Recommendation
The CADTH Canadian Drug Expert Committee (CDEC) recommends that adalimumab be reimbursed for the treatment of active moderate to severe hidradenitis suppurativa (HS) in adult patients who have not responded to conventional therapy (including systemic antibiotics) if the following clinical criterion and conditions are met:

### Clinical Criterion
1. Adult patients with active moderate to severe hidradenitis suppurativa with all of the following:
   - A total abscess and nodule count of 3 or greater
   - Lesions in at least two distinct anatomic areas, one of which must be Hurley Stage II or III
   - An inadequate response to a 90-day trial of oral antibiotics

### Conditions
1. Prescribed by a practitioner with expertise in the management of patients with HS.
2. Treatment with adalimumab should be discontinued if there is no improvement after 12 weeks of treatment.
3. Substantial reduction in price.

### Reasons for the Recommendation
1. Data from two placebo-controlled, double-blind, unpublished, phase III RCTs (PIONEER I and PIONEER II) demonstrated that in patients with active moderate to severe HS (Hurley Stage II or III), adalimumab treatment was associated with statistically significant improvements in health-related quality of life (HRQoL) measured using the DLQI, SF-36 (PCS) and EQ-5D compared to placebo after 12 weeks. Adalimumab was also associated with statistically significant reductions, compared to placebo, in the HiSCR (defined as at least a 50% reduction in abscess and inflammatory nodule count with no increase in abscess or draining fistula count relative to baseline) in both RCTs (42% and 59% of adalimumab-treated patients responded versus 26% and 28% of placebo-treated patients in PIONEER I and II, respectively). In addition, adalimumab treatment was associated with reductions in

various lesion counts, skin pain, and improvement in the modified Sartorius score (MSS). Overall, the safety and tolerability profile of adalimumab in HS does not appear to differ from that previously observed with adalimumab in other indications, with the exception of the reporting of hidradenitis as an AE in this patient population.

2. Based on the pharmacoeconomic evaluation submitted by the manufacturer, there was substantial uncertainty (attributed to the model design and the assumptions regarding discontinuations and transition probabilities) regarding the cost effectiveness of adalimumab for patients with moderate or severe hidradenitis suppurativa. CDR could only partially address these limitations to estimate an incremental cost per QALY gained for adalimumab compared with supportive care of $377,516.

**Of Note:**
CDEC noted that in the RCTs included in the clinical review, a treatment response was defined as at least a 50% reduction in inflammatory nodule (AN) count with no increase in abscess count or draining fistula count relative to baseline at week 12. The committee suggested that these criteria would be appropriate for establishing discontinuation criteria for HS patients who fail to respond to adalimumab.

**Background:**
Hidradenitis suppurativa (HS) is a chronic, debilitating, inflammatory skin disease of the hair follicles characterized by painful recurrent nodules and abscesses most commonly found in the apocrine gland areas of the body. The inflamed lesions produce recurrent purulent discharge and unpleasant odour and can lead to sinus tracts, scarring, strictures, or fistulas. HS is associated with considerable negative psychosocial impact and morbidity including obesity, pain, depression, and a lower health-related quality of life (HRQoL) than other dermatologic diseases.

Adalimumab (Humira) is a recombinant fully human immunoglobulin (IgG1) monoclonal antibody that binds to tumour necrosis factor (TNF)-$\alpha$, thus preventing binding to the TNF-$\alpha$ receptor and blocking its biological effects. Increased levels of TNF are found in HS lesions. Humira is approved in Canada for the treatment of active moderate to severe HS in adults who have not responded to conventional therapy (including systemic antibiotics). Humira is also approved in Canada for the treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, adult and pediatric Crohn's disease, ulcerative colitis, and chronic moderate to severe psoriasis. It is available as a 40 mg/0.8 mL sterile solution for subcutaneous (sc) injection. Dosage recommendations for the treatment of adult patients with HS are an initial induction dose of 160 mg, followed by 80 mg two weeks later, and then maintenance dosing with 40 mg every week beginning four weeks after the initial dose.[6]

**Summary of CDEC Considerations:**
CDEC considered the following information prepared by CDR: a systematic review of RCTs and pivotal studies of adalimumab, a summary of pharmacoeconomic information prepared by CDR, and patient group–submitted information about outcomes and issues important to patients with HS.

**Patient Input Information:**
Two patient groups, the Canadian Skin Patient Alliance and HS Aware, responded to the CDR call for patient input. Information in their submissions was collected via a bilingual questionnaire, patient testimonial videos, an HS patient meeting, conversation threads within social media platforms, website story submission platforms, and personal interviews. CDEC heard the following.

HS is a chronic and recurring dermatological condition, with patients experiencing painful, debilitating, and unsightly boils in the armpits, groin, between the buttocks, or under the breasts. As a result, patients experience physical pain, psychological distress, deep embarrassment, social isolation, and strained or broken relationships.

Caregivers help dress wounds, drive patients to appointments, and assist with more daily chores, including bathing an adult child who had to return home. Caregivers may feel an emotional burden due to not being able to help their loved ones and the economic burden of having to pay for non-reimbursed treatments or wound-care supplies.

Antiseptics, antibiotics, retinoids, steroids and photo-dynamic therapy are currently used to manage HS, with limited effect. Surgery can provide relief of varying durations and completeness, but it can cause scarring and infection.

Patients hope adalimumab will decrease pain and improve their quality of life, specifically less wound care, less itching, fewer visits to emergency departments, a greater ability to work, to hug and hold their children, and to regain intimacy and confidence. They also hope it will result in greater freedom to caregivers. A substantial majority of the patients who had used adalimumab reported quite positive results.

***Clinical Trials***
Two placebo-controlled, double-blind, unpublished, phase III randomized controlled trials (RCTs) met the selection criteria for inclusion in the systematic review: PIONEER I (N=307) and PIONEER II (N=326). The trials enrolled adult patients who had a diagnosis of HS and lesions in two or more distinct areas, at least one of which was Hurley Stage II or III, an abscess and inflammatory nodule (AN) count of three or more and who had an inadequate response to a 3-month trial of oral antibiotics. The primary efficacy endpoint was the proportion of patients who achieved HS clinical response (HiSCR), which was defined as at least a 50% reduction in AN count with no increase in abscess count or draining fistula count relative to baseline at week 12.

**Efficacy**
Key efficacy outcomes identified in the review protocol were quality of life and healthcare resource utilization. Other efficacy outcomes included counts of abscesses, nodules, scarring, and draining fistulas, infections, symptoms, mental health/psychological well-being, functional capacity/productivity, caregiver burden, and disease worsening.

***Quality of Life***
The mean DLQI scores at Week 12 were reduced, relative to baseline scores, by -5.4 and -5.1 points in adalimumab-treated patients compared to -2.9 and -2.3 points in placebo-treated patients, in PIONEER I and II, respectively. Between-group differences (i.e., -2.5 points in PIONEER I and -2.8 points in PIONEER II) were statistically significant in all patient group comparisons in both trials. Between-group differences did not exceed the MCID in any patient

group (i.e., all patients or those stratified by Hurley Stage II or III at baseline), but adalimumab-treated patients stratified by Hurley Stage II at baseline in PIONEER I did exhibit an improvement that was equivalent to the MCID (i.e., -3.3 points). At Week 12, mean HSQoL scores increased, relative to baseline, in both the adalimumab arms [redacted] and [redacted] points) and placebo arms ([redacted] and [redacted] points) in the PIONEER I and II trials, respectively. Between-group differences were statistically significant in the all patient group comparisons in both PIONEER I ([redacted] points) and PIONEER II ([redacted] points), and in patients classified as Hurley Stage II in PIONEER I ([redacted] points) and by Hurley Stage III in PIONEER II ([redacted] points).

At Week 12, the mean change from baseline in the PCS score of the SF-36 was +4.2 points in adalimumab-treated patients compared to +1.5 points in placebo-treated patients. The between-group difference ([redacted] points) was statistically significant and exceeded the general MCID. The mean change from baseline in the MCS score was [redacted] points in adalimumab-treated patients compared to +1.3 points in placebo-treated patients, [redacted] For all other domain scores, between-group differences were not statistically significant with the exception of higher summary scores for bodily pain and general health in the adalimumab arm compared to the placebo arm.

At Week 12, the between-group differences for the mean EQ-5D index score (i.e., [redacted] for all comparisons) was statistically significant in all patients, as well as in those patients stratified [redacted] For the EQ-5D VAS scores, the between-group mean differences ranged from [redacted].

***Health Care Utilization***

No data were available for healthcare resource utilization (i.e., physician visits, surgeries), with the exception of incision and drainage procedures. Overall, differences in the number of patients requiring interventions were not statistically significant in either of the PIONEER trials.

***HiSCR***

For all comparisons (i.e., all patients or those stratified by Hurley Stage II or Hurley Stage III at baseline) between-group differences in the proportion of patients who achieved HiSCR were statistically significantly larger with adalimumab compared to placebo in both trials. For all patients, the proportion of adalimumab-treated patients who achieved HiSCR was 58.9% (PIONEER II) compared with 41.8% (PIONEER I), despite similar proportions of placebo-treated patients reaching HiSCR in the two trials (i.e., 26.0% and 27.6%, respectively). Between-group differences were 31.5% (PIONEER II) and 15.9% (PIONEER I). The proportion of patients achieving HiSCR was statistically significantly greater in adalimumab-treated patients as early as Week 2 and remained statistically significant at Weeks 4, 8 and 12 in both PIONEER trials.

***AN count***

The proportion of patients who achieved an AN count of 0, 1, or 2 at Week 12 was 20.4% in PIONEER II and 7.4% in PIONEER I, and these results were statistically significant in favour of adalimumab for all comparisons in PIONEER II but only in patients stratified as Hurley Stage III at baseline in PIONEER I.

***MSS***

In PIONEER II, the between group difference in the change in MSS from baseline to Week 12 was statistically significant in favour of adalimumab for all patient comparisons (i.e., all patients

or those stratified by Hurley Stage II or III at baseline) whereas in PIONEER I the between-group differences were not statistically significant in any patient comparison.

**Harms**

The most frequent treatment-emergent AEs were hidradenitis, headache and nasopharyngitis. Similar proportions of patients experienced the same pattern of treatment-emergent AEs across treatment groups. The proportions of patients with serious adverse events (SAEs) (i.e. 2.0% and 1.8% of adalimumab-treated patients and 3.3% and 3.7% of placebo-treated patients) or withdrawals due to adverse events (WDAEs) (i.e. 0.7% and 2.5% and 2.0% and 4.3%, respectively) in PIONEER I and II, were low in both adalimumab- and placebo-treated patients in Period A. Overall, the safety and tolerability profile of adalimumab in HS does not appear to be different from that previously observed with adalimumab in other indications, with the exception of the reporting of hidradenitis as an AE in this patient population (i.e., which was considered to be an exacerbation of the underlying disease).

***Cost and Cost-Effectiveness***

Adalimumab is available as a syringe of 40 mg/0.8 ml solution for subcutaneous injection at a price of $740.36 per syringe. At the recommended dose of 160 mg initially (week 0), followed by 80 mg at week 2, then 40 mg at week 4, and 40 mg weekly thereafter, the annual cost per patient of adalimumab is $39,979 in the first year and $38,499 thereafter.

The manufacturer submitted a cost utility analysis to assess the cost effectiveness of adalimumab + supportive care (SC) compared with SC alone (which includes topical therapies, antiseptic washes, wound care dressings, oral antibiotics, analgesics, intralesional corticosteroid injections, incision and drainage procedures) in adults with moderate to severe HS who have had inadequate response to conventional systemic HS therapies (including systemic antibiotics). The analysis is based on a Markov model estimating long term health care costs and quality adjusted life years (QALYs) over a ten-year time horizon, from the perspective of the Canadian public health care payer. Health states were based on response as defined as a percentage reduction in abscess and inflammatory nodule count obtained from the PIONEER I and II clinical trials. The manufacturer reported that adalimumab was associated with greater QALYs and higher costs than SC, with an incremental cost utility ratio (ICUR) of $62,794 per QALY gained.

CDR identified the following limitations with the manufacturer's pharmacoeconomic submission:

- Assumptions relating to modeling transition probabilities beyond treatment discontinuation lack face validity and biased results in favor of adalimumab.
- Some assumptions particularly regarding use of resources by health state, nurse costs, compliance rates, rules for discontinuation including discontinuation based on frequency of assessment appeared to be biased in favour of adalimumab.
- A major error within the model pertained to the descriptions of health states based on an individual's health state relative to their previous health rather than their absolute health status, which are inappropriate for modelling. Given that patients would have very different baseline health states, patients within a given state within the Markov model may have very different symptoms. To partially address this, a CDR reanalysis was conducted over a 36-week time horizon, using the utility values obtained from the clinical trials.

Addressing the above limitations led to a CDR best estimate of $377,516 per QALY gained. With this scenario, a 90% price reduction for adalimumab is needed for an ICUR of $40,297 per QALY.

**CDEC Members:**
Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeysundera.

**April 20, 2016 Meeting**

**Regrets:**
None

**Conflicts of Interest:**
One member of CDEC did not participate in the discussion or voting due to a potential conflict of interest.

**About this Document:**
CDEC 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 CDEC made its recommendation. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

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

The Final CDEC 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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