Ontario Association of Gastroenterologists
Consensus Statement on the Ontario Reimbursement Criteria for Biologic Therapies in Inflammatory Bowel Disease

1.0 Executive Summary

The Ontario Association of Gastroenterologists (OAG) and the Ontario Public Drug Plan (OPDP) have a common goal of providing excellence in health care to patients living with inflammatory bowel disease (IBD). With this in mind, the OAG formed a consensus group to review the current Exceptional Access Program (EAP) reimbursement criteria (updated August 1, 2015) for the use of biologic therapies in IBD in Ontario. Taking into consideration recent treatment guidelines and the most robust clinical data for all available therapies, this group developed several recommendations that will further align the EAP criteria with current evidence.

In brief, the OAG recommends the following key changes to the current EAP reimbursement criteria for biologics in IBD:

- **Removal of the requirement for mandatory prior treatment with immunosuppressants or antibiotics**
- **Removal of thiopurines as an immunosuppressant option because of their recognized toxicity and new data showing poor efficacy**
- **Addition of the opportunity for dose optimization; dose increases should be approved on the basis of therapeutic dose monitoring (TDM) or objective evidence of improved disease control after dose escalation; efficacy should be reassessed periodically.**
    - **For infliximab in Crohn's disease (CD) and ulcerative colitis (UC): increase dose to a maximum of 10 mg/kg or increase dosing frequency to a maximum of every 4 weeks in patients with loss of response or shortening of the duration of response.**
    - **For adalimumab in CD: increase dose to 40 mg every week in patients who experience a disease flare.**
    - **The OAG recognizes the potential cost implications of dose escalation and would ensure that all changes were made on the basis of TDM or objective evidence of improved disease control (e.g., reduction of symptoms, inflammation) after escalation.**
- **Addition of access to early and/or ongoing biologic treatment in patients with UC who are hospitalized, recently discharged, and/or have severe disease.**

In addition, the OAG suggests some other important considerations:

- **The availability of a simple and standardized EAP form, similar to that used in other disease areas, would enable expedited approval of biologics for patients with IBD.**
- **The time to biologic approval should be shortened to align with those in other Canadian jurisdictions.**

This document provides details regarding these key changes, additional recommendations, and the evidence that supports their implementation.

2.0 Overview

The Ontario Association of Gastroenterologists (OAG) and the Ontario Public Drug Program (OPDP) Exceptional Access Program (EAP) share several common goals: to provide patients with access to the most effective therapies, to optimize use of constrained health care resources, and to achieve overall excellence in health care in Ontario. The OAG believes that an update to the current EAP criteria for the reimbursement of biologics in inflammatory bowel disease (IBD) will help achieve these goals and will result in the best possible outcomes for these patients.

Anti-tumor necrosis factor (TNF) biologics have proven efficacy in the treatment of moderate to severe cases of Crohn's disease (CD) and ulcerative colitis (UC). These agents demonstrate strong evidence in terms of achieving the key goals of treatment, such as steroid-free remission, symptom resolution, mucosal healing, and improved quality of life. However, access to these products varies considerably across Canada, primarily as a result of differing drug plan processes and reimbursement criteria.

Numerous changes have occurred within the treatment landscape of IBD since the OPDP's EAP criteria for biologics were first established:

- Publication of the Canadian Association of Gastroenterology's (CAG) Guidelines for Patients Hospitalized with Severe UC and the UC Toronto Consensus Clinical Practice Guidelines (Bitton et al., 2012; Bressler et al., 2015).
- Development of CAG Guidelines for CD (currently in progress; anticipated in fall 2016)
- Improved understanding of the limited efficacy and safety issues associated with thiopurines
- Decisions in other Canadian jurisdictions to not require thiopurine exposure
- Availability of long-term evidence for the efficacy and safety of anti-TNF biologics
- Emergence of therapeutic dose monitoring (TDM) as a strategy to optimize efficacy and make earlier decisions regarding biologic failure
- Evidence for the benefits of dose optimization and changes to the infliximab and adalimumab product monographs

While the implications of some of these changes are reflected in the most recent update of the EAP criteria (August 1, 2015), the OAG suggests that consideration of several others could make a substantial impact on clinical outcomes in patients with IBD. In addition to clinical benefits, improved access to medication could yield several economic benefits, such as reduced hospitalization and disability and improved productivity.

In June of 2016, an OAG consensus group convened to review the current OPDP EAP reimbursement criteria for biologics in IBD. Taking into consideration recent changes in treatment guidelines and the most robust clinical data for all available agents, the consensus group developed several

recommendations that will improve the alignment of these criteria with current evidence (**Section 3.0**). The consensus group also considered other topics related to the approval and availability of biologic agents for IBD and proposed several additional considerations (**Section 4.0**). These recommendations and their supporting evidence are summarized below.

3.0 Recommended Changes to EAP Criteria by Disease Area

3.1 Crohn's Disease

Infliximab (REMICADE®) and adalimumab (HUMIRA®) are currently the only two biologic therapies reimbursed for the treatment of moderate to severe Crohn's Disease (CD) in Ontario (OPDP, 2015). As described below, clinical data supporting the use of these anti-TNF drugs are available from randomized controlled trials (RCTs) and other supportive studies conducted in patients with luminal or fistulizing CD. Current reimbursement criteria from the OPDP EAP vary between these two patient groups (OPDP, 2015). The consensus group's recommended changes to these criteria are presented below, with support provided by recent clinical evidence.

3.1.1 Luminal Crohn's Disease

Numerous RCTs have demonstrated the value of infliximab and adalimumab in the treatment of moderate to severe luminal CD. When used as an induction modality, these biologics can result in symptom improvement and clinical remission (Targan et al., 1997; Hanauer et al., 2002; Hanauer et al., 2006; Colombel et al., 2007; Sandborn et al., 2007b; Rutgeerts et al., 2012; Watanabe et al., 2012). Similarly, regular maintenance dosing of infliximab or adalimumab can sustain clinical remission, reduce the need for corticosteroid therapy, and lower the risk of disease-related hospitalization and surgery (Hanauer et al., 2002; Rutgeerts et al., 2004; Colombel et al., 2007; Hyams et al., 2007; Sandborn et al., 2007a; Feagan et al., 2008; Rutgeerts et al., 2012; Watanabe et al., 2012).

As detailed in **Table 2.1** (see pg. 7), current OPDP EAP reimbursement criteria for the use of biologics in moderate to severe luminal CD require the following (OPDP, 2015):

- Harvey Bradshaw Index (HBI) ≥7; AND
- Failure to respond to conventional treatment with glucocorticoid therapy; AND
- Failure to respond to an immunosuppressive agent (e.g., azathioprine, 6-mercaptopurine, methotrexate, or cyclosporine) tried for ≥3 months.

The criteria additionally present specific dosing regimens for the use of infliximab and adalimumab in the treatment of CD (**Table 2-1**) (OPDP, 2015).

The consensus group strongly suggests the following changes to the current OPDP EAP criteria for luminal CD:

1) **Definitions of patients who are corticosteroid resistant and corticosteroid dependent should be updated to align with recent Canadian clinical practice guidelines.**
    - The Toronto Consensus Guidelines for the medical management of nonhospitalized patients with UC provide clear definitions of these patient subgroups (Bressler et al., 2015):
        - Corticosteroid resistant: lack of symptomatic response despite a course of oral prednisone of 40 to 60 mg/day (or equivalent) for a minimum of 14 days.
        - Corticosteroid dependent: inability to withdraw (within 3 months of initiation) oral corticosteroid therapy without recurrence of symptoms, a symptomatic relapse within 3 months of stopping corticosteroid therapy, or the need for 2 or more courses of corticosteroid therapy within one year.

2) **The requirement of three months prior immunosuppressive therapy should be removed by changing the word "AND" to "OR".**
    - Although azathioprine and 6-mercaptopurine are commonly used for the treatment of IBD, neither therapy is indicated for such use and both are associated with limitations in terms of safety and efficacy (Marshall et al., 2014).
        - Use of these therapies is associated with an elevated risk of hepatosplenic T-cell lymphoma (HSTCL), a rare but aggressive and often fatal cancer (Thai and Prindiville, 2010).
        - In 2014, Health Canada issued a safety alert regarding the use of azathioprine and mercaptopurine and the risk of HSTCL, and recommended specifically against their use as monotherapy for the treatment of IBD (Health Canada, 2014); the current EAP criteria contradict this guidance, putting prescribers at substantial medico-legal risk.
        - Both therapies are associated with other serious adverse events (AEs), such as myelosuppression, hepatotoxicity, pancreatitis, allergic reactions, and opportunistic infections (Kornbluth et al., 2010).
        - A meta-analysis of 13 RCTs found that azathioprine and 6-mercaptopurine offered no advantage over placebo for induction of remission or clinical improvement of CD, and that azathioprine was inferior to infliximab for induction of steroid-free remission (Chande et al., 2013).
        - Similarly, a network meta-analysis (NMA) of 39 trials reported that azathioprine and 6-mercaptopurine did not differ from placebo for induction of remission in CD (Hazlewood et al., 2015).
            - While infliximab + azathioprine and adalimumab were found to be the most effective therapies for the induction and maintenance of remission of CD, concerns have been expressed regarding the validity of NMA in this

therapeutic area because of clinical heterogeneity between studies (NICE, 2015).

- The SONIC study of patients with moderate to severe CD demonstrated lower rates of clinical remission and mucosal healing with azathioprine alone than with both infliximab alone and infliximab + azathioprine combination therapy (Colombel et al., 2010).
- The AZTEC and RAPID studies demonstrated that azathioprine was no more effective than placebo or conventional management for the achievement of remission in patients with recently diagnosed CD (Cosnes et al., 2013; Panes et al., 2013).
- The 2009 Canadian Association of Gastroenterology (CAG) anti-TNF Clinical Practice Guidelines state that "the slow onset of action of [azathioprine and 6-mercaptopurine] limits their effectiveness for patients with acute symptoms in whom a rapid therapeutic response is required," (Sadowski et al., 2009).

o Limited evidence is available for methotrexate, which is also not indicated for use in moderate to severe CD and may be toxic to some patient subgroups.

- Efficacy and safety results for methotrexate are only available from relatively small (38–150 patients) and in some cases weakly designed (e.g., inappropriate dosing, open-label, underpowered) clinical trials (McDonald et al., 2014; Swaminath et al., 2014).
  - Findings from these trials and those from meta-analyses remain mixed in terms of its value in CD (Feagan et al., 1995; Oren et al., 1997; Arora et al., 1999; Feagan et al., 2000; Mate-Jimenez et al., 2000; Khan et al., 2011; Laharie et al., 2011; McDonald et al., 2014; Patel et al., 2014; Kopylov et al., 2016).
- Poor consensus exists across current treatment guidelines regarding the appropriate use of methotrexate in CD.
  - The American Gastroenterological Association Institute states that methotrexate is no more effective than placebo for the induction of remission in CD, but may be effective in maintaining remission (Dassopoulos et al., 2013; Terdiman et al., 2013).
  - European guidelines suggest that methotrexate should generally be reserved for the treatment of active or relapsing CD in patients who are refractory to or intolerant of thiopurines and/or anti-TNF therapy (Dignass et al., 2010; Mowat et al., 2011).
- No formal dose-finding studies of methotrexate have been conducted in patients with IBD (Herfarth et al., 2016).
- Relatively few patients (<10%) receive methotrexate in current clinical practice, as evidenced by data from clinical trials and an observational registry (TREAT) (Hanauer et al., 2002; Hanauer et al., 2006; Hyams et al., 2007; Dassopoulos et al., 2013).

- In a prospective study of patients with CD, only 11% of methotrexate-treated patients achieved mucosal healing compared with 60% of infliximab-treated patients (P = 0.008) (Laharie et al., 2011).
- The product monograph for methotrexate notes that it can cause fetal death, embryotoxicity, abortion, or teratogenic effects when administrated to a pregnant woman; it is therefore not recommended for women of childbearing potential and thus exposure should not be required prior to initiation of biologic therapy (Pfizer Canada, 2011).

- Cyclosporine is also not indicated for moderate to severe CD and is associated with poor efficacy and safety concerns.
  - In a placebo-controlled, double-blind RCT, cyclosporine was not associated with long-term improvement of active chronic CD (Brynskov et al., 1991).
  - Other studies similarly report no advantage of cyclosporine compared with conventional treatments when used alone or in combination (Feagan et al., 1994; Nicholls et al., 1994; Feagan, 1995; Stange et al., 1995), and that relapse is expected after discontinuation (Santos et al., 1995).
  - Evidence supporting an elevated risk of nephrotoxicity has raised concerns regarding its use (Lobo and Feagan, 1990; Sternthal et al., 2008).

- Reimbursement criteria for biologics in other Canadian jurisdictions, such as British Columbia (BC) and Manitoba (MB), do not require prior use of immunosuppressant therapy in patients with luminal CD.

3) **The opportunity for dose optimization of biologic therapy should be added to address cases of lost response or shortening of response duration. Dose increases should be approved on the basis of TDM or objective evidence of improved disease control** (e.g., reduction of symptoms, inflammation) **after dose escalation. Efficacy should be reassessed periodically.**
   - A consensus statement on the management of CD from the European Crohn's and Colitis Organisation states the following: "For active disease, reduction of the interval between doses, or dose escalation are appropriate strategies before switching to another agent," (Dignass et al., 2010).
   - For infliximab:
     - Retrospective studies demonstrate that increasing the dose of infliximab or shortening the dosing interval between infusions (i.e., to 4 or 6 weeks) can be effective strategies to rescue treatment response in up to 96% of patients (Regueiro et al., 2007; Chaparro et al., 2011; Kopylov et al., 2011; Chaparro et al., 2012; Katz et al., 2012; Steenholdt et al., 2015).
     - Results from the TAXIT study suggest that use of TDM to adjust serum infliximab concentrations (e.g., within a window of 3 to 7 µg/mL via dose escalation) can reduce the risk of relapse and the need for rescue therapy compared with adjustments based on clinical features (Vande Casteele et al., 2015).

        - Additional support for TDM is provided by the following:
            - A retrospective study of patients with IBD, in which mean infliximab levels were found to be significantly higher in patients in remission than in those with disease flare (Marits et al., 2014).
            - A recent Canadian clinician's guide (Khanna et al., 2013).
        - The Canadian product monograph for infliximab states the following for patients with luminal CD: "For patients who have an incomplete response, consideration may be given to adjusting the dose up to 10 mg/kg," (Janssen Pharmaceuticals, 2015a).
    - For adalimumab:
        - A systematic review of 39 studies of adalimumab in CD found that dose escalation permitted response to be regained in 71.4% of patients and that remission was achieved in 39.9% of patients (Billioud et al., 2011).
        - A large (N = 720), multicenter, real-world study similarly reported that dose escalation re-induced response for ≥6 months in 67% of patients with CD (Baert et al., 2013).
        - The Canadian product monograph for adalimumab states the following for patients with CD: "For patients who experience a disease flare, dose escalation may be considered," (AbbVie Pharmaceuticals, 2016). Escalation to 40 mg weekly is supported by numerous studies (Wolf et al., 2014; Dubinsky et al., 2016).

A detailed summary of the current OPDP EAP reimbursement criteria for luminal CD and the consensus group's recommended changes is presented in **Table 2-1**.

Table 2-1: Current OPDP EAP reimbursement criteria for luminal CD and recommended changes from the consensus group

Product Name (BRAND, generic)	Dosage Form & Strength	Current Reimbursement Criteria	Standard Approval Duration	Recommended Changes to Current Reimbursement Criteria
REMICADE®, infliximab	100 mg/ 10 mL IV infusion	Treatment of **moderate to severe (luminal) CD** in patients who have: • HBI score ≥7*; AND • Failed to respond to conventional treatment with glucocorticoids (prednisone 40 mg/day or equivalent for at least weeks or dose cannot be tapered to below prednisone 20 mg/day or equivalent; AND • Failed to respond to an immunosuppressive agent (azathioprine, 6-mercaptopurine, methotrexate, or cyclosporine) tried for at least 3 months *Note: any intolerance(s) or contraindication(s) to treatment with required alternative(s) must be described in detail.* *If the patient has HBI <7, the request will be reviewed by external medical experts when the following information is provided: blood work (with Hct, Hb, CRP, ESR, platelets, and ferritin levels); supporting endoscopy; details of weight loss; and a list of narcotic analgesics being used. **Renewal** will be considered for patients with 50% reduction in HBI from pretreatment as well as improvement of symptoms (e.g., absence of bloody diarrhea and weight stabilization or increase) and no longer using steroids. Biochemical improvements may also be required. The planned dosing regimen for the requested biologic should be provided. The recommended doses for the treatment of CD are as follows: • Infliximab: 5 mg/kg/dose at 0, 2, and 6 weeks, then 5 mg/kg/dose every 8 weeks • Adalimumab: 160 mg at week 0; 80 mg at week 2; followed by 40 mg every 2 weeks.	Initial: 3 months First renewal: 1 year Second and subsequent renewals: 2 years	Treatment of moderate to severe (luminal) CD in patients who have: • HBI score ≥7*; AND • **Corticosteroid resistance (lack of symptomatic response despite course of oral prednisone 40-60 mg/day [or equivalent] for a minimum of 14 days or corticosteroid dependence (inability to withdraw [within 3 mths of initiation] oral corticosteroid therapy without a recurrence of symptoms, symptomatic relapse within 3 mths of stopping corticosteroids, or need for ≥2 course of corticosteroids within 1 year, OR** • Failed to respond to an immunosuppressive agent (methotrexate or cyclosporine) tried for at least 3 months *Note: any intolerance(s) or contraindication(s) to treatment with required alternative(s) must be described in detail.* *If the patient has HBI <7, the request will be reviewed by external medical experts when the following information is provided: blood work (with Hct, Hb, CRP, ESR, platelets, and ferritin levels); supporting endoscopy; details of weight loss; and a list of narcotic analgesics being used. Renewal will be considered for patients with 50% reduction in HBI from pretreatment as well as improvement of symptoms (e.g., absence of bloody diarrhea and weight stabilization or increase) and no longer using steroids. Biochemical improvements may also be required. The planned dosing regimen for the requested biologic should be provided. The recommended doses for the treatment of CD are as follows: • Infliximab: 5 mg/kg/dose at 0, 2, and 6 weeks, then 5 mg/kg/dose every 8 weeks. **May increase to 10 mg/kg or increase frequency to every 4 weeks if there is a loss of response or shortening of the duration of response to treatment. Dose increases should be approved on the basis of TDM[a] or objective evidence of improved disease control after dose escalation; efficacy should be reassessed periodically.**
HUMIRA®, adalimumab	40 mg/ 0.8 ml prefilled syringe and 40 mg/ 0.8 mL prefilled pen for SQ injection			

Product Name (BRAND, generic)	Dosage Form & Strength	Current Reimbursement Criteria	Standard Approval Duration	Recommended Changes to Current Reimbursement Criteria
				• Adalimumab: 160 mg at week 0; 80 mg at week 2; followed by 40 mg every 2 weeks; **increase dose to 40 mg every week in patients who experience a disease flare.**
KEY: CD = Crohn's disease; CRP = C-reactive Protein; EAP = Exceptional Access Program; ESR = Erythrocyte Sedimentation Rate; Hb = Hemoglobin; HBI = Harvey Bradshaw Index; Hct = Hematocrit; IV = intravenous; OPDP = Ontario Public Drug Plan; SQ = subcutaneous; TDM = therapeutic dose monitoring				

[a] EAP criteria already require TDM to explain dose increases.

Note: proposed changes appear in bold or by omission of text in the right-most column; no changes are recommended for the standard approval duration.

Source: OPDP, (2015).

3.1.2 Peri-anal and Fistulizing Crohn's Disease

Relatively strong evidence supports the efficacy of infliximab and adalimumab in the treatment of peri-anal and fistulizing CD. Infliximab has demonstrated clinical improvements within dedicated RCTs (Present et al., 1999; Sands et al., 2004) and other supportive studies (Cohen, 2001; Rasul et al., 2004; Rodrigo et al., 2004), while adalimumab has shown efficacy within the CHARM RCT, observational studies, and in a case series (Colombel et al., 2007; Hinojosa et al., 2007; Cordero Ruiz et al., 2011; Tonelli et al., 2012). In contrast, very limited evidence is available from small and typically uncontrolled studies to support the use of any other agents in the treatment of peri-anal and fistulizing CD. Updated CAG clinical practice guidelines for the use of anti-TNF biologics in CD are anticipated in fall 2016. However, current OPDP EAP reimbursement criteria require failure on antibiotic AND immunosuppressive therapy before initiation of biologic therapy (**Table 2-2**) (OPDP, 2015).

The consensus group recommends that the current reimbursement criteria for peri-anal and fistulizing CD be modified as follows:

1) **Use of antibiotic and immunosuppressive therapy should be eliminated as a prerequisite for initiation of biologic therapy.**
    - Randomized, placebo-controlled studies including large series of patients remain lacking for antibiotic therapies in peri-anal and fistulizing CD (Sica et al., 2014).
        - Results from small RCTs and uncontrolled cases series demonstrate limited efficacy that rarely includes complete and/or sustained healing; further, bothersome side effects are associated with long-term use (Bernstein et al., 1980; Brandt et al., 1982; Jakobovits and Schuster, 1984; Solomon et al., 1993; Thia et al., 2009; ECCO, 2014; Sica et al., 2014; Klag et al., 2015).
    - As noted for luminal CD, Health Canada issued a safety alert in 2014 regarding use of azathioprine and mercaptopurine and the risk of HSTCL, recommending specifically against their use as monotherapy for treatment of IBD (Sadowski et al., 2009; Health Canada, 2014; Marshall et al., 2014); current EAP criteria contradict this guidance, putting prescribers at substantial medico-legal risk.
    - Other serious AEs (e.g., myelosuppression) have been associated with use of azathioprine and mercaptopurine (Kornbluth et al., 2010).
    - Similar to antibiotics, the safety and efficacy of azathioprine and 6-mercaptopurine have not been demonstrated in rigorous RCTs including large populations of patients with peri-anal and fistulizing CD.
    - Other Canadian jurisdictions (e.g., BC, MB) do not require prior use of antibiotics and/or immunosuppressives before initiation of biologic therapy.

2) **For the purpose of renewing therapy, a positive response should be defined as either resolution OR improvement of fistulae, rather than just resolution.**
    - Patients with partially healed fistulae (improvement) remain in need of ongoing maintenance therapy to potentially achieve the key goal of treatment, complete fistula closure/remission (Klag et al., 2015; Marzo et al., 2015).
    - Prescribing information for infliximab from the United States Food and Drug Administration states that the treatment is indicated for "reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing disease," (Janssen Pharmaceuticals, 2015b).
    - As perianal fistulas are associated with considerable impairment of quality of life (QoL) related to pain, discharge, incontinence, disability, and disfigurement, it is reasonable to expect that an improvement could lead to important reductions in disabling symptoms and potentially improve QoL (Cadahia et al., 2004; Michetti, 2009; Klag et al., 2015; Marzo et al., 2015).

3) **As for luminal CD, the opportunity for dose optimization of biologic therapy should be added to address loss of response or shortening of response duration in patients with fistulizing CD. Dose increases should be approved on the basis of TDM or objective evidence of improved disease control** (e.g., reduction of symptoms, inflammation) **after dose escalation (Khanna et al., 2013; Vande Casteele et al., 2015). Efficacy should be reassessed periodically.**
    - For infliximab:
        - In the ACCENT II study, most patients with fistulizing CD who lost their response to infliximab 5 mg/kg and re-established response after dose escalation to infliximab 10 mg/kg did so after one dose and all had done so after two doses (Sands et al., 2004; Janssen Pharmaceuticals, 2015a).
        - The Canadian product monograph for infliximab states the following for patients with fistulizing CD: "For patients who respond and then lose their response, consideration may be given to treatment with 10 mg/kg," (Janssen Pharmaceuticals, 2015a).
    - For adalimumab:
        - A systematic review of 39 studies of adalimumab in CD found that dose escalation permitted response to be regained in 71.4% of patients and that remission was achieved in 39.9% of patients; >20 of the studies included patients with fistulizing CD (Billioud et al., 2011).
        - The Canadian product monograph for adalimumab states the following for patients with CD: "For patients who experience a disease flare, dose escalation may be considered," (AbbVie Pharmaceuticals, 2016).

A detailed summary of the current OPDP EAP reimbursement criteria for peri-anal fistulizing CD and the consensus group's recommended changes is presented in **Table 2-2**.

Table 2-2: Current OPDP EAP reimbursement criteria for peri-anal and fistulizing CD and recommended changes from the consensus group

Product Name (BRAND, generic)	Dosage Form & Strength	Reimbursement Criteria	Standard Approval Duration	Recommended Changes	
				Reimbursement Criteria	Standard Approval Duration
REMICADE®, infliximab	100 mg/ 10 mL IV infusion	**Treatment of fistulizing CD** in patients who have: • Actively draining perianal or enterocutaneous fistula(e) that have recurred or persisted despite a course of antibiotic therapy (ciprofloxacin and/or metronidazole) AND immunosuppressive therapy (azathioprine or 6-mercaptopurine) *Note: any intolerance(s) or contraindication(s) to treatment with required alternative(s) must be described in detail.* **Renewal** will be considered for patients with resolution of fistulae. The planned dosing regimen for the requested biologic should be provided. The recommended dose for the treatment of CD is 5 mg/kg/dose at 0, 2, and 6 weeks followed by 5 mg/kg/dose every 8 weeks.	Initial: 3 months First renewal: 1 year Second and subsequent renewals: 2 years	Treatment of fistulizing CD in patients who have: **Actively draining perianal or enterocutaneous fistula(e) with minimal luminal disease activity** Renewal will be considered for patients with resolution **or improvement**[a] of fistulae**.** The planned dosing regimen for the requested biologic should be provided. The recommended dose for the treatment of CD is 5 mg/kg/dose at 0, 2, and 6 weeks followed by 5 mg/kg/dose every 8 weeks. **May increase to 10 mg/kg or increase frequency to every 4 weeks if there is a loss of response or shortening of the duration of response to treatment. Dose increases should be approved on the basis of TDM**[b] **or objective evidence of improved disease control after dose escalation; efficacy should be reassessed periodically.**	Initial: 3 months **Renewal: 1 year unless in remission**

Product Name (BRAND, generic)	Dosage Form & Strength	Reimbursement Criteria	Standard Approval Duration	Recommended Changes	
				Reimbursement Criteria	Standard Approval Duration
HUMIRA®, adalimumab	40 mg/ 0.8 mL prefilled syringe and 40 mg/ 0.8 mL prefilled pen for SQ injection	**For the treatment of fistulizing CD with concomitant luminal disease in patients who meet the following criteria:** • Patients with actively draining perianal or enterocutaneous fistula(e) that have recurred or persist despite a course of appropriate antibiotic therapy (e.g., ciprofloxacin and/or metronidazole) AND immunosuppressive therapy (e.g., azathioprine or 6-mercaptopurine) AND • HBI score ≥7 The dose that will be considered is adalimumab (HUMIRA®) 160 mg at week 0, 80 mg at week 2, followed by 40 mg every 2 weeks. **Renewal** will be considered based on the response to therapy. The dose that will be considered on renewals is adalimumab (HUMIRA®) 40 mg every two weeks. All requests for higher doses will not be approved.	Initial: 3 months Renewal: 3 months to 1 year pending fistula resolution; Second renewal: 2 years for second renewal of requests with complete resolution; Case-by-case duration for renewal of requests with partial resolution	For the treatment of fistulizing CD with concomitant luminal disease in patients who meet the following criteria: • Patients with actively draining perianal or enterocutaneous fistula(e) AND • HBI score ≥7 The dose that will be considered is adalimumab (HUMIRA®) 160 mg at week 0, 80 mg at week 2, followed by 40 mg every 2 weeks. Renewal will be considered based on the response to therapy. The dose that will be considered on renewals is adalimumab (HUMIRA®) 40 mg every two weeks. **Increase dose to 40 mg every week in patients who experience a disease flare.**	Initial: 3 months Renewal: 3 months to 1 year **unless in remission (*no additional criteria*)**
KEY: CD = Crohn's disease; HBI = Harvey Bradshaw Index; IV = intravenous; OPDP = Ontario Public Drug Plan; SQ = subcutaneous					

[a] The consensus group recommends that "improvement" be defined as a decrease from baseline in the number of open draining fistulas of ≥50% for at least two consecutive visits that must be at least four weeks apart.

[b] EAP criteria already require TDM to explain dose increases.

Note: proposed changes appear in bold or by omission of text in the two right-most columns.

Source: OPDP, (2015).

3.2 Ulcerative Colitis

The treatment of UC varies by level of disease activity, which is typically categorized as mild, moderate, or severe using the Mayo score (Schroeder et al., 1987). Infliximab is currently the only biologic therapy that is publically reimbursed for the treatment of UC in Ontario. Evidence for its efficacy and safety is provided by studies (clinical trials and meta-analyses) of patients with moderate to severe disease who had failed to respond to or were receiving corticosteroids (Rutgeerts et al., 2005; Lawson et al., 2006; Ford et al., 2011; Lv et al., 2014).

The consensus group wishes to emphasize that ambulatory and hospitalized patients with UC represent very different patient groups that have distinct treatment needs.

- Separate guidelines have been developed for the treatment of these patients (Bitton et al., 2012; Bressler et al., 2015).
- Improved treatment of patients with moderate to severe ambulatory disease, including earlier and appropriate use of biologic therapies, could help avert hospitalization, colectomy, and early mortality, and reduce costs (Reinisch et al., 2012).
- Hospitalized patients require urgent consideration and treatment; early escalation to second-line medical therapy with infliximab or cyclosporine should be considered (Bitton et al., 2012; Gibson et al., 2015).

The current OPDP EAP criteria for the use of biologics in UC vary by level disease activity (OPDP, 2015). **The consensus group agrees that the current reimbursement criteria for induction of remission in mild UC accurately reflect the best available clinical evidence for this population (see Table 2-3, pg. 16). The consensus group also agrees that biologics should be used for the treatment of moderate or severe disease in patients who have failed two weeks[a] (14 days) of prednisone or who cannot decrease their prednisone dose without having a relapse of symptoms. However, the consensus group suggests the following changes to the criteria for induction of remission in patients with moderate or severe disease:**

1) **The time frame for intravenous steroid use should be shortened from 1 week to 3 days in hospitalized patients.**
    - As highlighted throughout the Toronto Consensus Guidelines and by others, corticosteroid-free remission is a key goal of treatment in UC (Reinisch et al., 2012; Bressler et al., 2015)
    - Reduction of the duration of intravenous therapy from 1 week to 3 days is consistent with current guidelines for the treatment of hospitalized patients (Bitton et al., 2012)
    - Toxicity has been observed with both short- and long-term treatment with corticosteroids, presenting as bothersome and/or serious AEs such as moon face, hirsutism, hypertension, new onset diabetes mellitus, infection, osteonecrosis,

[a] Note: recommended to change wording to "14 days" in criteria to align with recent guidelines (Bressler et al., 2015)

myopathy, psychosis, among others (Kusunoki et al., 1992; Marshall and Irvine, 1997; Mahadevan, 2004; Dignass et al., 2010); treatment of these AEs is associated with a considerable economic burden (Manson et al., 2009; Sarnes et al., 2011).

- Such toxicity and costs further underscore the importance of limiting the duration of treatment.

2) **Biologic therapy should be initiated if the patient cannot taper their prednisone dose without symptom relapse.**
   - Infliximab has demonstrated efficacy in the induction and maintenance of steroid-free remission, as well as symptom control, mucosal healing, and reductions in serious complications (e.g., colectomy) and hospitalization (Rutgeerts et al., 2005; Sandborn et al., 2009); accordingly, earlier use may improve clinical outcomes.
     - An expert consensus group has stated that "using infliximab earlier in the course of disease may improve the likelihood of achieving treatment goals," (Reinisch et al., 2012).

3) **For patients with moderate or severe UC, the use of thiopurines should be removed from all induction criteria.**
   - The Toronto Consensus Guidelines recommend against the use of thiopurine monotherapy to induce complete remission (Bressler et al., 2015).
   - Evidence supporting the use of azathioprine in UC is limited (Reinisch et al., 2012):
     - One meta-analysis of five RCTs suggested that the probability of treatment success with azathioprine was similar to or only marginally improved compared with that of aminosalicylates or placebo (Leung et al., 2008; Reinisch et al., 2012).
     - In the UC SUCCESS study, infliximab and azathioprine were associated with similar rates of corticosteroid-free remission; however, azathioprine was associated with significantly lower rates of Mayo score response and mucosal healing and a higher rate of AEs (Panaccione et al., 2014)
   - As discussed for CD, Health Canada issued a safety alert in 2014 regarding use of azathioprine and mercaptopurine and the risk of HSTCL, recommending specifically against their use as monotherapy for treatment of IBD (Health Canada, 2014; Marshall et al., 2014); current EAP criteria contradict this guidance, putting prescribers at substantial medico-legal risk.
   - Other serious AEs have been associated with the use of thiopurines in UC (e.g., pancreatitis, bone marrow suppression) (Dignass et al., 2012).
   - Other Canadian jurisdictions (e.g., BC, Alberta, and Saskatchewan) do not require prior use of immunosuppressives before initiation of biologic therapy.

4) **Once discharged, hospitalized patients who were initiated on biologic therapy should have access to ongoing induction treatment at doses received in hospital, which may be higher than doses required for ambulatory patients**
    - Patients with acute severe UC (ASUC) have faster clearance rates for anti-TNF biologics because of higher serum and mucosal TNF burden, and may require either higher or more frequent dosing than ambulatory patients to optimize exposure (Rosen et al., 2015).
    - Acceleration of the induction dosing frequency of infliximab in hospitalized patients with ASUC is associated with a significantly reduced need for early colectomy compared with standard dosing regimens (at 0, 2 and 6 weeks) (Gibson et al., 2015).

The consensus group agrees that the current reimbursement criteria for biologic maintenance therapy in UC accurately reflect the best available clinical evidence; however, adjustments should be made to the requirements for approval and dosing:

1) **For simplification of administrative processes, approval should be provided for three maintenance doses. Patients should then be assessed between Weeks 12 and 14, with subsequent approval provided for 12 months if appropriate** (Janssen Pharmaceuticals, 2015a).

2) **As for CD, the opportunity for dose optimization of biologic therapy should be added to address loss of response or shortening of response duration. Dose increases should be approved on the basis of TDM or objective evidence of improved disease control** (e.g., reduction of symptoms, inflammation) **after dose escalation. Efficacy should be reassessed periodically.**
    - Evidence from retrospective studies suggests that dose escalation or shorter time intervals between infusions can rescue response in patients with UC (Yamada et al., 2014; Dumitrescu et al., 2015; Janssen Pharmaceuticals, 2015a).
    - Dose escalation should be initiated early for patients who are hospitalized, recently discharged, or with severe disease, given evidence for more rapid drug clearance in patients with severe UC and their high short-term risk of colectomy (Ananthakrishnan et al., 2010; Kevans et al., 2012; Targownik et al., 2012; Gibson et al., 2015).
    - The Canadian product monograph for infliximab states the following for patients with UC: “In some adult patients, consideration may be given to adjusting the dose up to 10 mg/kg to sustain clinical response and remission,” (Janssen Pharmaceuticals, 2015a).

A detailed summary of the current OPDP EAP reimbursement criteria for UC and the consensus group’s recommended changes is presented in **Table 2-3**.

Table 2-3: Current OPDP EAP reimbursement criteria for UC and recommended changes from the consensus group

Product Name (BRAND, generic)	Dosage Form & Strength	Reimbursement Criteria	Standard Approval Duration	Recommended Changes	
				Reimbursement Criteria	Standard Approval Duration
REMICADE®, infliximab	100 mg/ 10 mL IV infusion	**Treatment of UC disease** in patients who meet the following criteria: **<u>Induction</u>** **1. Mild disease** a. Mayo score <6, AND b. Patients with mild disease will be considered on a case-by-case basis but submission must include the rationale for coverage. **2. Moderate disease** a. Mayo score between 6 and 10 (inclusive), AND b. Endoscopic[a] subscore of 2, AND c. Failed 2 weeks of oral prednisone ≥40 mg (or IV equivalent for at least 1 week) AND 3 months of AZA/6-MP (or where the use of immunosuppressants is contraindicated), OR d. Stabilized with 2 weeks of oral prednisone ≥40 mg (or a 1 week course of IV equivalent) but the prednisone dose cannot be tapered despite 3 months of AZA/6MP (or where the use of immunosuppressants is contraindicated). **3. Severe disease** a. Mayo score >10, AND b. Endoscopy[a] subscore ≥2, AND c. Failed 2 weeks of oral prednisone ≥40 mg (or 1 week IV equivalent), OR d. Stabilized with 2 weeks of oral prednisone ≥40 mg (or 1 week of IV equivalent) but the prednisone dose cannot be tapered despite 3 months of AZA/6MP (or where the use of immunosuppressants is contraindicated).	Initial: 3 months 5 mg/kg/dose at 0, 2, and 6 weeks Renewal duration: 3 months to 1 year (pending if patient continues on steroids) Second and subsequent renewal: 2 years (for those off steroids)	Treatment of UC disease in patients who meet the following criteria: <u>Induction</u> 1. Mild disease a. Mayo score <6, AND b. Patients with mild disease will be considered on a case-by-case basis but submission must include the rationale for coverage. 2. Moderate disease a. Mayo score between 6 and 10 (inclusive), AND b. Endoscopic[a] subscore of 2, AND c. Failed **14 days** of oral prednisone ≥40 mg (or IV equivalent for at least **3 days**), OR d. Stabilized with **14 days** of oral prednisone ≥40 mg (or a **3-day** course of IV equivalent) but the prednisone dose cannot be tapered **without a relapse of symptoms.** 3. Severe disease a. Mayo score >10, AND b. Endoscopy[a] subscore ≥2 c. Failed **14 days** of oral prednisone ≥40 mg (or **3 days of** IV equivalent), OR d. Stabilized with **14 days** of oral prednisone ≥40 mg (or **3 days** of IV equivalent) but the prednisone dose cannot be tapered **without a relapse of symptoms.**	Initial: 3 months 5 mg/kg/dose at 0, 2, and 6 weeks

Product Name (BRAND, generic)	Dosage Form & Strength	Reimbursement Criteria	Standard Approval Duration	Recommended Changes	
				Reimbursement Criteria	Standard Approval Duration
		Maintenance 1. After **3 loading doses** of REMICADE®: a. Mayo score <6, AND b. 50% reduction in prednisone from the starting dose. *Approval: 3 months at 5 mg/kg/dose every 8 weeks* If patient is completely off steroids: *Approval: 12 months at 5 mg/kg/dose every 8 weeks* 2. Subsequent renewals: a. Mayo score <6, AND b. Must be off steroids. (Patients who remain on steroids will be considered on a case-by-case basis) *Approval: 12 months at 5 mg/kg/dose every 8 weeks*		Maintenance 1. After 3 loading doses of REMICADE®: a. Mayo score <6, AND b. 50% reduction in prednisone from the starting dose. 2. Subsequent renewals: a. Mayo score <6, AND b. Must be off steroids. (Patients who remain on steroids will be considered on a case-by-case basis)	***First 3 doses at 5 mg/kg/dose; assessment between Weeks* 12 and 14; approval for 12 months** 12 months at 5 mg/kg/dose every 8 weeks **May increase to 10 mg/kg or increase frequency to every 4-6 weeks if there is a loss of response or shortening of the duration of response to treatment.** **Dose increases should be approved on the basis of TDM[b] or objective evidence of improved disease control after dose escalation; efficacy should be reassessed periodically.**
KEY: AZA = azathioprine; IV = intravenous; 6MP = 6-mercaptopurine; OPDP = Ontario Public Drug Plan; UC = ulcerative colitis					

[a] The endoscopy procedure must be done within the last year but does not have to be full endoscopy.

[b] EAP criteria already require TDM to explain dose increases.

Note: proposed changes appear in bold or by omission of text in the two right-most columns.

Source: OPDP, (2015).

4.0 Additional Considerations

The OAG consensus group discussed a number of additional topics related to the approval and availability of/access to biologics in IBD. Inflammatory bowel disease is associated with a substantial disease burden in Canada, including both high per patient costs and prevalence rates – in 2012, there were an estimated 233,000 Canadians living with IBD, resulting in approximately $1.2 billion in direct medical costs (Rocchi et al., 2012). Since the introduction of anti-TNF biologic therapies in 2005, the annual incidence rate for colectomy has consistently declined in Canadian UC patients (Reich et al., 2014). However, there is a marked delay in access to anti-TNF therapies among publicly-covered Canadian IBD patients: in comparison with private-coverage patients, the median time interval between prescription and administration is approximately 11 days longer. This delay is associated with significantly increased hospitalization rates, with approximately three times as many ER visits and IBD-related admissions in patients with public coverage (Rumman et al., 2016).

One key topic was the need for a simple and standardized EAP form that would streamline the approval process. Such forms are currently available in other therapeutic areas, providing clear specifications regarding reimbursement requirements and thereby expediting patient approval and access to biologic therapies. The OAG believes that the availability of such a form for biologics in IBD would significantly improve patient outcomes, and is willing to work with the OPDP to develop this document.

The OAG also discussed the imminent availability of two additional drugs for the treatment of UC: adalimumab (HUMIRA®) and vedolizumab (ENTYVIO®). Both of these therapies have received positive recommendations from the Canadian Agency for Drugs Technologies in Health's (CADTH) Common Drug Review (CDR) and are currently undergoing pricing negotiations with the PCPA. As it is anticipated that these drugs will be available in late 2016 and/or early 2017, the OAG notes that the EAP reimbursement criteria may soon need to be updated to consider these new options for UC.

Finally, the OAG additionally discussed the opportunities and challenges associated with the introduction of subsequent entry biologics (SEBs) in Canada. They noted that while open competition between SEBs and innovator biologics will improve affordability and increase treatment options, several concerns surround the approval and use of SEBs. In particular, the OAG was concerned about the extrapolation of SEB data from other indications to IBD, the interchangeability/switching of SEBs, immunogenicity, and naming conventions. Recognizing the importance of these topics, the OAG has developed a separate document that summarizes these considerations and recommends solutions that will ensure the safe and effective introduction of SEBs for IBD.

5.0 Conclusions

In summary, the OAG and the OPDP share the common goals of improving patient care and optimizing use of health care resources. Review of the most robust data for the treatment of IBD suggests that several modifications could be made to the current EAP criteria that would improve their alignment with current evidence. The OAG consensus group has presented several targeted recommendations that, if implemented, could increase access to biologic therapies and provide more optimized treatment. Further, they have recognized several issues—such as the need for a standardized EAP form for biologic use in IBD and the imminent availability of new innovator and SEB products—that will bear impact on the EAP criteria, patient access, and treatment outcomes. The OAG hopes to work together with the OPDP to improve the standard of care for patients living with IBD in Ontario.

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