Common Drug Review
Subsequent Entry Biologic Review Report

November 2017

Drug	Inflectra (infliximab)
Indication	• Adults with moderately to severely active Crohn's disease • Adults with fistulizing Crohn's disease • Adults with moderately to severely active ulcerative colitis
Listing request	For each indication, list in a similar manner to the public plan listing criteria for Remicade
Dosage form(s)	Intravenous infusion (powder for solution, 100 mg/vial)
NOC date	June 10, 2016
Manufacturer	Hospira, a Pfizer Company

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH).

Through the CADTH Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update — Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

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ABBREVIATIONS

5-ASA	5-aminosalicylic acid
ACPM	Advisory Committee on Prescription Medicines
ADA	anti-drug antibodies
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
AS	ankylosing spondylitis
ATI	anti-infliximab antibodies
CCC	Crohn's and Colitis Canada
CD	Crohn's disease
CDAI	Clinical/Crohn's Disease Activity Index
CDC	complement-dependent cytotoxicity
CDEC	Canadian Drug Expert Committee
CDR	Common Drug Review
CSR	Clinical Study Report
CTD	Common Technical Documents
DMARD	disease-modifying antirheumatic drug
EAP	Exceptional Access Program
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicine Agency
EU	European Union
FCD	Fistulizing Crohn's disease
FDA	Food and Drug Administration
GI	gastrointestinal
HCP	residual host cell protein
HMW	high molecular weight
IBD	inflammatory bowel disease
IGF-1	recombinant insulin-like growth factor 1
IgG1	chimeric human-murine immunoglobulin G1
IL	interleukin
IRR	infusion-related reaction
LD50	lethal dose 50
LOCF	last observation carried forward
LPS	lipopolysaccharide
LRV	log10 reduction value
MAH	Marketing Authorization Holder
MLR	mixed lymphocyte reaction
MMP	matrix metalloproteinase
MSS	Mayo scoring system
MTX	methotrexate
NDS	New Drug Submission
NK	natural killer
NOC	Notice of Compliance
PBMC	peripheral blood mononuclear cell

PBRER	periodic benefit-risk evaluation report
PK	pharmacokinetic
PsA	psoriatic arthritis
PsO	plaque psoriasis
PSUR	Periodic Safety Update Report
RA	rheumatoid arthritis
RCT	randomized controlled trial
SAE	serious adverse event
SCCAI	Simple Clinical Colitis Activity Score
SD	standard deviation
SEB	subsequent entry biologic
SOC	system organ class
SNDS	Supplemental New Drug Submission
sTNF alpha	soluble tumour necrosis factor alpha
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TGA	Therapeutic Good Administration
tmTNF alpha	transmembrane tumour necrosis factor alpha
TNF alpha	tumour necrosis factor alpha
TNFR	TNF receptor
UC	ulcerative colitis
US	United States

EXECUTIVE SUMMARY

Approach to the Review

The CADTH Common Drug Review (CDR) approach to reviewing Inflectra followed the *CDR Procedure and Submission Guidelines for Subsequent Entry Biologics* (March, 2014). The CDR team reviewed the information provided by the manufacturer regarding product information, indications under review, the manufacturer's requested listing criteria, biosimilarity, extrapolation, and cost. Clinical Study Reports and published articles were also appraised. Reviewers provided a critical appraisal of the clinical evidence, a discussion of extrapolation from the indications of rheumatoid arthritis (RA) and ankylosing spondylitis (AS) to inflammatory bowel disease (IBD), and an evaluation of cost.

Product Information

Inflectra (CT-P13; infliximab) is a subsequent entry biologic (SEB) based on the reference infliximab product (Remicade). Inflectra has been approved in Canada for the following indications:

- Use in combination with methotrexate (MTX) for the reduction in signs and symptoms, inhibition of the progression of structural damage, and improvement in physical function in adult patients with moderately to severely active RA.
- Reduction of signs and symptoms and improvement in physical function in patients with active AS who have responded inadequately to, or are intolerant to, conventional therapies.
- Reduction of signs and symptoms, induction of major clinical response, and inhibition of the progression of structural damage of active arthritis, and improvement in physical function in patients with psoriatic arthritis (PsA).
- Treatment of adult patients with chronic, moderate to severe plaque psoriasis (PsO) who are candidates for systemic therapy. For patients with chronic, moderate PsO, Inflectra should be used after phototherapy has been shown to be ineffective or inappropriate.
- Reduction of signs and symptoms, induction and maintenance of clinical remission and mucosal healing and reduction of corticosteroid use in adult patients with moderately to severely active Crohn's disease (CD) who have had an inadequate response to a corticosteroid and/or aminosalicylate. Inflectra can be used alone or in combination with conventional therapy.
- Treatment of fistulizing CD (FCD), in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment.
- Reduction of signs and symptoms, induction and maintenance of clinical remission and mucosal healing, and reduction or elimination of corticosteroid use in adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response to conventional therapy (i.e., aminosalicylate and/or corticosteroid and/or an immunosuppressant).

The manufacturer is requesting that Inflectra be reimbursed for adults with CD, FCD, and UC. The indications for RA, AS, PsO, and PsA were previously reviewed by CDR in 2015.

Clinical Evidence

CT-P13 PMS (post-marketing surveillance) is an ongoing (four year) phase IV, open-label, single arm study of CT-P13 for all approved indications in South Korea. An interim analysis was conducted in adults with moderately to severely active CD (N = 83), FCD (N = 12), and moderately to severely active UC (N = 78) across 15 study centres in South Korea with follow-up of 30 weeks. CT-P13 was administered every 8 weeks (± 5 days) after induction therapy of three 5 mg/kg doses at weeks 0, 2, and 6. Most patients (59.0%) received doses of 5 mg/kg. Higher doses of 5 mg/kg to 10 mg/kg were administered to

41% of patients. The efficacy analysis set consisted of patients who received at least one dose of CT-P13 and had at least one assessment following baseline (N=145, 83.8%). All patients were included in the safety analyses. Outcomes of clinical response, remission, disease control, need for rescue medication, and safety were reported for patients with CD, FCD, and UC as well as mucosal healing for patients with UC.

Based on last observation carried forward (LOCF) imputation, among CD infliximab-naive patients, 31/39 (79.5%) achieved clinical response and 23/39 (59.0%) achieved clinical remission at week 30. Among CD patients who were switched from Remicade to CT-P13, 25/31 (80.6%) achieved remission throughout visits two to six and 27/31 (87.1%) patients did not experience disease worsening. In FCD infliximab-naive patients, 2/6 (33.3%) achieved clinical response and 1/6 (16.7%) achieved clinical remission. In FCD patients switched from Remicade to CT-P13, clinical remission and disease control was achieved in only one patient at visit six. In UC infliximab-naive patients, 39/54 (72.2%) achieved clinical response and 20/54 (37.0%) achieved clinical remission at week 30. Among UC patients who were switched from Remicade to CT-P13, 5/11 (45.5%) achieved remission throughout visits two to five and no patients experienced disease worsening. Based on complete case analysis of UC infliximab-naive patients, 9/13 (69.2%) experienced mucosal healing at week 30 while 6/9 (66.7%) patients who were switched from Remicade to CT-P13 experienced mucosal healing throughout visits two to five. The manufacturer also submitted data to Health Canada suggesting similar incidences of clinical response and remission at weeks 14 and 30 for CD and UC, and mucosal healing for UC, among treatment-naive patients in the CT-P13 PMS study and patients from previously conducted Remicade studies. A total of 51 treatment-emergent adverse events (TEAEs) in 38 patients occurred in CT-P13 PMS. There were no notable differences in TEAEs between patients who were infliximab-naive (23.9%) and those who switched from Remicade (18.3%). No malignancies, pneumonia, deaths, or any other events of special interest were observed during the 30-week interim period.

The CT-P13 PMS study is limited by its uncontrolled observational design, small sample size, absence of important efficacy outcomes, such as extra-intestinal manifestations, disease biomarkers, quality of life, and immunogenicity, and short duration of follow-up (30-week interim analysis). The generalizability of the observed outcomes in patients from South Korea to Canadian patients with IBD is uncertain.

Other Studies: CT-P13 4.1 is a small (N = 20) phase IV, ongoing (four year), open-label, single arm study conducted in adult patients with CD or UC in South Korea. An interim analysis of efficacy and safety in 10 patients ([redacted]) from [redacted] study centres was available for review. Other observational studies of CT-P13 in IBD, not sponsored by the manufacturer, have been conducted in cohorts from Norway, Hungary, the Czech Republic, and Korea. The manufacturer conducted a systematic literature search of randomized controlled trials (RCTs) and observational studies of the reference product Remicade, in patients with CD and UC. Rates of infusion-related reactions (IRRs), infections, pneumonia, tuberculosis, malignancies, and need for surgery or hospitalization were compared with rates from observational studies of CT-P13 (PMS + non-Celltrion sponsored studies). Safety data were generally similar between CT-P13 and the reference product, Remicade, in treatment-naive and switched patients combined for IRRs, pneumonia, tuberculosis, and malignancies. There were some differences between Remicade and CT-P13 for the rates of infection, rates of surgery, and disease-related hospitalization; however, the interpretation of the data is limited due to the differences in study design, study populations, and outcome definitions. Overall, data from cumulative post-marketing patient exposure to CT-P13 from October 2013 to December 2015 suggest that no new safety signals have emerged.

Extrapolation

CT-P13 (Inflectra) received market authorization in Canada in January 2014 for the indications of PsO and PsA based on the extrapolation of evidence from studies conducted in patients with RA and AS. Extrapolation was supported by similarities in the pathology of RA, AS, PsA, and PsO and the mechanism of action of all tumour necrosis factor alpha (TNF alpha) blockers in these indications. In June 2016, Health Canada approved CT-P13 for adult CD, FCD, and UC. The European Medicines Agency (EMA), the Food and Drug Administration (FDA), and the Australian Therapeutic Goods Administration have also approved CT-P13 for CD and UC.

In Health Canada's initial review of CT-P13 for all indications, some concerns about extrapolating data from studies conducted in patients with RA and AS to IBD were mentioned. These included differences in disease mechanisms between rheumatic and bowel diseases and higher risk of hepatosplenic T-cell lymphoma in patients with IBD treated with infliximab. The predominant form of TNF in RA and AS is soluble TNF alpha (sTNF alpha); whereas, in CD and UC, transmembrane TNF alpha (tmTNF alpha) plays an additional and central role. Also, unlike RA and AS, in bowel diseases antibody-dependent cell-mediated cytotoxicity (ADCC) is an important mechanism of action and is mediated by afucosylation and FcγIIIa receptor binding. Minor differences have been observed between CT-P13 and the reference product in FcγIIIa binding and ADCC activity using *in vitro* assays with natural killer (NK) cells from patients with CD and V/V or V/F FcγIIIa genotype (no difference observed with F/F genotype). In other assays using peripheral blood mononuclear cells (PBMCs) from patients with CD and V/F or F/F FcγIIIa genotype, no difference in ADCC activity was observed. In June 2016, Health Canada authorized the use of CT-P13 for the IBD indications based on extrapolation from previously submitted clinical studies in patients with RA and AS, comparable pharmacokinetics, and newly submitted physiochemical and biological data.[1]

Other considerations for the extrapolation of data between RA and AS, and IBD, include differences in treatment strategies between the indications, such as the use of concomitant medication, and the higher doses (> 5 mg/kg) of CT-P13 that may be used. In CT-P13 PMS, 41% of patients received doses higher than 5 mg/kg of CT-P13 and no notable dose-dependent differences in the distribution of TEAEs were observed between patients who received 5 mg/kg or patients who received > 5 mg/kg. However, the immunogenic similarity of the higher dose compared with a regular or higher dose of Remicade is uncertain.

Cost Comparison

The manufacturer's submitted price for Inflectra ($525.00 per 100 mg vial) is 47% lower than the price of infliximab ($987.56 per 100 mg vial), when using the Ontario Exceptional Access Program (EAP) price for infliximab.

Clinical Expert Comments[1]

The clinical expert consulted for this review noted that both private and public drug plans have guidelines in place that stipulate which patients are eligible for treatment with anti-TNF drugs, and CT-P13 will fit within that framework. The expert indicated that an important question, which will need to be addressed if the drug is introduced, is whether patients who are stable on the reference product,

[1] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

Remicade, will have their treatment substituted with CT-P13 or whether it will only be used in treatment-naive patients. Endoscopic evaluation of disease activity may be required in patients who experience a disease flare after switching, and there are significant barriers to that in terms of access to endoscopy. Currently, limited evidence is available to assess and predict patient response to switching from Remicade to CT-P13.

Conclusion

CT-P13 provides clinicians and patients with another potentially cost-effective choice of a biological drug for IBD. The focus of this CDR review of CT-P13 (Inflectra) is for the recently approved indications of CD, FCD, and UC in adult patients. The Notice of Compliance (NOC) for the CD, FCD, and UC indications was granted subsequent to an earlier NOC for CT-P13 for the indications of RA, AS, PsO, and PsA. Of note, Health Canada approved the indications of PsO and PsA based on the extrapolation of data from studies conducted with patients with RA and AS. All clinical evidence currently available for CT-P13 in patients with IBD is based on observational, open-label studies from Korea or Europe in small numbers of patients. The pivotal study, CT-P13 PMS, is an observational, open-label study conducted in South Korea in patients with IBD, with a 30-week interim analysis. Naive indirect comparisons of CT-P13 with studies of Remicade (infliximab) suggest similar efficacy and similar safety for some safety end points in patients with CD or UC. Nonetheless, in the absence of data from RCTs, the clinical similarity of CT-P13 and Remicade for IBD in the Canadian population remains uncertain. Given that the results of CT-P13 PMS are based on an interim analysis, the ongoing monitoring of CT-P13 in patients with IBD will be important for evaluating long-term efficacy and safety.

Note: References in square brackets [ ] indicate the references cited by the manufacturer, while the references cited by CDR are indicated by superscripts.

1. PRODUCT INFORMATION

1.1 Overview of the SEB Product

Hospira has a co-exclusive distribution agreement in place with Celltrion Healthcare Corporation whereby Celltrion Healthcare Corporation is the manufacturer of the infliximab biosimilar CT-P13, which is marketed under the Trade name INFLECTRA® or REMSIMA®. Celltrion Healthcare Corporation is the Marketing Authorization Holder (MAH) for REMSIMA® (infliximab; CT-P13) in a number of territories and Hospira is the MAH for INFLECTRA® (infliximab; CT-P13) in a number of territories, some of which overlap with Celltrion Healthcare Corporation. In the following sections of this template, CT-P13, INFLECTRA® and REMSIMA® all refer to the same molecule, the infliximab biosimilar manufactured by Celltrion. In Canada, Hospira has acquired the right to market and distribute INFLECTRA® (infliximab; CT-P13) from Celltrion Healthcare Corporation.

Characteristics	Manufacturer-Provided Details	
	INFLECTRA®	REMICADE®
Brand name:	INFLECTRA®	REMICADE®
Non-proprietary name:	Infliximab	Infliximab
Manufacturer:	Hospira Healthcare Co.	Janssen Inc.
Strength(s):	100 mg/vial	100 mg/vial
Dosage form:	Powder for Solution, Sterile, Lyophilized	Powder for Solution, Sterile, Lyophilized
Route of administration:	Intravenous Infusion	Intravenous Infusion
Drug Identification Number(s):	02419475	02244016
Therapeutic classification:	Biological Response Modifier	Biological Response Modifier
Excipients	Sucrose, sodium dihydrogen phosphate monohydrate, di-sodium hydrogen phosphate dihydrate, polysorbate 80. No preservatives are present.	Dibasic sodium phosphate dihydrate, monobasic sodium phosphate monohydrate, polysorbate and sucrose. No preservatives are present.
Impurities[a]	**Product-related** High molecular weight species: [redacted] Others: see Table below **Process-related** Residual host cell protein: [redacted] Residual host cell DNA: [redacted] (max) Residual Protein A: [redacted] Others: see section below	**Product-related** High molecular weight species: [redacted] Others: see Table below **Process-related** Not available, see explanation at the end of this section

Source: INFLECTRA® and REMICADE® product monographs
[a]Include both product and process-related impurities.
Please note that there have been no changes to the manufacturing of INFLECTRA® since the New Drug Submission (NDS) was filed to Health Canada in 2012, and subsequent NOC granted in 2014 for the RA, AS, PsA and PsO indications.

This means that, for the consideration of the current CDR submission for the indications of CD and UC, the pharmaceutical form, composition, dosage form, strength, route of administration, purity and impurities for INFLECTRA® remain the same as described in the first CDR INFLECTRA® submission and positive recommendation in 2014 for the RA, AS, PsA and PsO indications.

Therefore, for the remainder of Section 1.1 of the template, the same information that was submitted in the original INFLECTRA® CDR submission is being included. As for the product-related impurities, it was tested in the 3-way similarity studies and the results are in line with what was submitted in the original CDR submission (CTD Module 3.2.R). If more details are required on this section, the INFLECTRA® submission from 2014 should be consulted.

Pharmaceutical form: chimeric human-murine immunoglobulin G1 (IgG1) monoclonal antibody

Pharmaceutical composition: as the formulation of INFLECTRA® was set identical to that of REMICADE®, the dosage form for both products contain 100 mg infliximab, 500 mg sucrose, 0.5 mg polysorbate 80, 2.2 mg sodium dihydrogen phosphate monohydrate and 6.1 mg di-sodium hydrogen phosphate dihydrate. No preservatives are present.

Dosage form: both INFLECTRA® and REMICADE® are the same dosage form, namely formulated as white lyophilized powder.

Strength: both INFLECTRA® and REMICADE® are supplied in 100 mg vials to be reconstituted with 10 mL sterile water resulting in a final concentration of 10 mg/mL. For both products, the total dose of the reconstituted product must be further diluted to 250 mL with 0.9% Sodium Chloride Injection USP.

Route of administration: both INFLECTRA® and REMICADE® are administrated via intravenous infusion. (Please be advised that in the REMICADE® product monograph (p.3), route of administration is listed as i.v. injection, however, infusion is cited in the remaining of the document).

Purity and impurities:

Product-related impurities

Product-related impurities include: oxidized variants, deamidated variants, C-terminal lysine variants, glyco-variants, high molecular weight (HMW) species as well as molecular fragments.

A summary of the results for product-related impurity comparison between INFLECTRA® drug product and REMICADE® are presented in the table below.

Impurity	Test Method	Results
Oxidized variants	Peptide Mapping (liquid chromatography-mass-spectrometry; LC-MS)	• Based on the available data, it can be concluded that only very low and comparable amounts of oxidized molecular variants are present in IFT drug product and REMICADE®.
Deamidated variants	Ion-exchange chromatography-high performance liquid chromatography (IEC-HPLC)	[redacted]
C-lysine terminal variants	IEC-HPLC	• It was demonstrated that the difference observed between INFLECTRA® and REMICADE® with respect to the relative proportion (peak ratio) of the 6 IEC-HPLC peaks is attributable to C-terminal lysine variability. • However, it has been shown that C-terminal lysine variability holds no bearing on biological activity *in vitro*, and that C-terminal lysine clipping occurs rapidly both *in vitro* and *in vivo*, suggesting that nearly all infliximab molecules are fully clipped within several hours following dosing.

Impurity	Test Method	Results
Glyco-variants	Site Specific and N-Linked Glycan Analysis by Means of LC-MS Peptide Mapping; Oligosaccharide Profiling; Monosaccharide Analysis; Sialic Acid Analysis	• Asparagine 300 was shown to be the only site of N-glycosylation for both INFLECTRA® and REMICADE®. No O-linked glycans were detected, as one might expect for an IgG1 monoclonal antibody, for INFLECTRA® or the REMICADE®. • Both INFLECTRA® drug product and REMICADE® were shown to contain mostly G0F and G1F structures. Minor species including Man5, G2F, G0F minus N-acetylglucosamine, and G0 were detected. • HPAEC-PAD data reveal that the type and proportion of the uncharged glycans is conserved between INFLECTRA® and the REMICADE®. • The identified sugars were [redacted]; both INFLECTRA® and REMICADE® had similar molar ratios for the 4 sugars. • The molar ratio of neutral and amino sugars was observed to be highly similar for INFLECTRA® drug product and REMICADE®. • INFLECTRA® samples contain the same type as well as highly similar levels of sialic acid (expressed as molar ratios) when compared to REMICADE®.
High molecular weight species	Size exclusion chromatography (SEC)-HPLC	• INFLECTRA® drug product and REMICADE® samples contain prominently monomer drug substance within a comparable range ([redacted], respectively). The impurities are high molecular weight species, which are all [redacted] across both INFLECTRA® and REMICADE® products.
Molecular fragments	Capillary electrophoresis sodium dodecyl sulfate (CE-SDS) (Reduced/Non-Reduced)	• INFLECTRA® and REMICADE® display the same types of IgG fragments. • INFLECTRA® drug product and REMICADE® have similar amount of intact IgG ([redacted], respectively)

Process-related impurities

Process-related impurities include: residual host cell protein (HCP), host cell DNA, residual Protein A, recombinant Insulin-Like Growth Factor 1 (IGF-1), recombinant human insulin and Pluronic F-68. A brief summary of these results can be found below.

i. In terms of HCP, the level that was detected across [redacted] is generally considered as an acceptable level for therapeutic proteins.
ii. The level of residual host cell DNA, [redacted], below the acceptance criterion of ≤4 ppb (pg/mg) at release.
iii. The range of residual Protein A [redacted], below the limit of ≤4 ppm (ng/mg).
iv. The ability of the INFLECTRA® purification process to clear IGF-1 and recombinant insulin was evaluated as part of a spiking study. The study demonstrated that the capability of clearance by specific a chromatography [redacted] (Log_{10} reduction value) for IGF-1 and [redacted].
v. [redacted]

[redacted].

For REMICADE®, the process-related impurities and their clearance is specific to each manufacturing process, therefore, Celltrion (manufacturer of INFLECTRA®) does not have information on the manufacturing process of REMICADE® and the tests used to demonstrate clearance of the impurities in that process. It is also technically inappropriate to apply a Celltrion impurities test to REMICADE® to generate this data. The approach is therefore for the biosimilar company to develop the manufacturing process and control strategy to remove process-related impurities and to maintain the impurities at the lowest possible level to meet the regulatory requirement. Process-related impurities such as residual host cell protein, residual DNA, and endotoxin all fit this approach. Due to these reasons, there are no regulatory agencies requesting this comparative analysis.

1.2 Overview of the Reference Product

The reference product described in this submission is REMICADE® (Infliximab; Powder for Solution, Sterile, Lyophilized, 100 mg/vial). REMICADE® is currently authorized for sale and marketing in Canada (DIN: 02244016).

The infliximab drug substance is a chimeric IgG1κ antibody 1328 amino acids in length that is composed of human constant and murine variable regions. Infliximab neutralizes the biological activity of human TNFα by binding with high affinity to the soluble and transmembrane forms of TNFα (sTNFα, and tmTNFα) and inhibits their binding to TNF receptors (TNFRs).

In Canada, REMICADE® (infliximab) is indicated for:

1. use in combination with MTX for the reduction in signs and symptoms, inhibition of the progression of structural damage and improvement in physical function in adult patients with moderately to severely active RA.
2. the reduction of signs and symptoms and improvement in physical function in patients with active AS who have responded inadequately, or are intolerant to, conventional therapies.
3. reduction of signs and symptoms, induction and maintenance of clinical remission and mucosal healing and reduction of corticosteroid use in adult patients with moderately to severely active CD who have had an inadequate response to a corticosteroid and/or aminosalicylate. REMICADE® can be used alone or in combination with conventional therapy.
4. reduction of signs and symptoms and induction and maintenance of clinical remission in pediatric patients with moderately to severely active CD who have had an inadequate response to conventional therapy (corticosteroid and/or aminosalicylate and/or an immunosuppressant). The safety and efficacy of REMICADE® is not established in patients less than 9 years of age.
5. treatment of FCD, in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment.
6. reduction of signs and symptoms, induction and maintenance of clinical remission and mucosal healing, and reduction or elimination of corticosteroid use in adult patients with moderately to severely active UC who have had an inadequate response to conventional therapy (i.e., aminosalicylate and/or corticosteroid and/or an immunosuppressant).
7. reduction of signs and symptoms, induction and maintenance of clinical remission, and induction of mucosal healing in pediatric patients with moderately to severely active UC who have had an inadequate response to conventional therapy (i.e., aminosalicylate and/or corticosteroid and/or an immunosuppressant). The safety and efficacy of REMICADE® have not been established in patients less than 6 years of age.

8. reduction of signs and symptoms, induction of major clinical response, and inhibition of the progression of structural damage of active arthritis, and improvement in physical function in patients with PsA.
9. treatment of adult patients with chronic moderate to severe PsO who are candidates for systemic therapy. For patients with chronic moderate PsO, REMICADE® should be used after phototherapy has been shown to be ineffective or inappropriate. When assessing the severity of psoriasis, the physician should consider the extent of involvement, location of lesions, response to previous treatments, and impact of disease on the patient's quality of life.

2. INDICATIONS

2.1 Health Canada-Approved Indications

Indication(s)	Extrapolation
• use in combination with methotrexate for the reduction in signs and symptoms, inhibition of the progression of structural damage and improvement in physical function in adult patients with moderately to severely active rheumatoid arthritis.	No
• the reduction of signs and symptoms and improvement in physical function in patients with active ankylosing spondylitis who have responded inadequately, or are intolerant to, conventional therapies.	No
• reduction of signs and symptoms, induction of major clinical response, and inhibition of the progression of structural damage of active arthritis, and improvement in physical function in patients with psoriatic arthritis.	Yes
• treatment of adult patients with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy. For patients with chronic moderate plaque psoriasis, INFLECTRA® should be used after phototherapy has been shown to be ineffective or inappropriate. When assessing the severity of psoriasis, the physician should consider the extent of involvement, location of lesions, response to previous treatments, and impact of disease on the patient's quality of life.	Yes
• reduction of signs and symptoms, induction and maintenance of clinical remission and mucosal healing and reduction of corticosteroid use in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to a corticosteroid and/or aminosalicylate. INFLECTRA® can be used alone or in combination with conventional therapy	Yes
• treatment of fistulizing Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment.	Yes
• reduction of signs and symptoms, induction and maintenance of clinical remission and mucosal healing, and reduction or elimination of corticosteroid use in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy (i.e., aminosalicylate and/or corticosteroid and/or an immunosuppressant).	Yes

3. MANUFACTURER'S REQUESTED LISTING CRITERIA

3.1 Requested Listing Criteria

Requested Listing Criteria
• List in a similar manner to the public plan listing criteria for REMICADE®. • *Alternatively*: reduction of signs and symptoms, induction and maintenance of clinical remission and mucosal healing and reduction of corticosteroid use in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to a corticosteroid and/or aminosalicylate. INFLECTRA® can be used alone or in combination with conventional therapy.
• List in a similar manner to the public plan listing criteria for REMICADE®. • *Alternatively*: treatment of fistulising Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment.
• List in a similar manner to the public plan listings criteria for REMICADE®. • *Alternatively*: reduction of signs and symptoms, induction and maintenance of clinical remission and mucosal healing, and reduction or elimination of corticosteroid use in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy (i.e., aminosalicylate and/or corticosteroid and/or an immunosuppressant).

3.2 Rationale for Requested Listing Criteria

The over-arching rationale for the requested listing criteria for all indications listed below is based on the principle of demonstrated biosimilarity between INFLECTRA® and the currently reimbursed reference medicinal product, REMICADE®. First, the formulation of INFLECTRA® has been designed to replicate that of REMICADE® and both drug products are identical with respect to strength, pharmaceutical form, route of administration, and composition in excipients (see Section 1.1 above). Second, the active substance of INFLECTRA®, infliximab, has been developed as a similar biological medicinal product to that of the active substance of REMICADE® (infliximab). Specifically, an extensive series of orthogonal methods were designed to compare the physiochemical properties as well as the biological activities of INFLECTRA® and REMICADE®, and results clearly demonstrated that the active substance is highly similar between these two products (see Section 4.1 for detailed information).

In 2014, the Canadian Drug Expert Committee (CDEC) issued a positive recommendation for INFLECTRA® for the PsA and PsO indications via extrapolation. Similarly, the data to support the CD and UC indications for INFLECTRA® via extrapolation is based on the totality of the evidence collected from the quality, non-clinical, and clinical comparability exercise. Please see below in Section 6 for Manufacturer's rationale, as well as International Regulatory Conclusions to support the CD and UC indications via extrapolation.

Currently, infliximab (REMICADE®) is reimbursed by all CDR-participating drug plans across the country for the treatment of CD (see Appendix 2). Consequently, we anticipate that INFLECTRA® will also be reimbursed under the same clinical criteria as REMICADE® from these CDR-participating drug plans, assuming that the CDEC issues a positive recommendation for INFLECTRA® for CD.

Currently, 5 of the CDR participating drug plans reimburse infliximab (REMICADE®) for the UC indication. In these 5 provinces, we anticipate INFLECTRA® will also be reimbursed under the same clinical criteria as REMICADE®, assuming that the CDEC issues a positive recommendation for INFLECTRA® for UC.

The CDR-participating drug plans that do not currently reimburse REMICADE® for UC may find that significant cost savings associated with using INFLECTRA® may take this opportunity to expand treatment options to the patients who require treatment for this indication.

Assuming a positive Health Canada and CDEC recommendation for these indications, the requested listing criteria are reasonable and justified.

4. BIOSIMILARITY

4.1 Quality Information

A product characterization exercise was conducted previously using a range of state-of-the-art methodologies to demonstrate comparability between CT-P13 and European Union (EU) approved REMICADE®. The results of these 2-way similarity studies comparing CT-P13 with EU-approved REMICADE® were presented in the previous CDR submission in (CTD Module 3.2.R.5) of the initial Submission. Subsequently, a wide range of orthogonal test methods were performed to determine comparability of CT-P13 and REMICADE® in a 3-way study (CTD Module 3.2.R-reg-info document) using EU and United States (US) approved REMICADE®. These studies included an extensive comparative analysis of primary, secondary and tertiary structure, glycan profiles and of post-translational modifications as well as comparative stability studies. In addition, many biological assays have been included to evaluate similarity in all biological activities associated with known and putative functions and therapeutic effects. The analytical methods and biological assays used in similarity studies have been suitably validated or qualified to provide a high level of assurance that the methods could detect any slight differences and are scientifically sound, fit for purpose, reliable and reproducible.

Similarity was previously demonstrated in terms of primary structure, secondary and higher order structure as well as similar disulfide bonding. This information was included in the original CDR Submission for INFLECTRA® as part of the Common Technical Documents (CTD). For ease of reference, the same CTD documents are included in this section, and the information can be found in the CTD 3.2.R-reg document (Modules 3.2.R.2.2, 3.2.R.2.3.1, 3.2.R.2.3.2, 3.2.R.2.3.3, 3.2.R.2.3.4, 3.2.R.2.3.5 and 3.2.R.2.3.6).

Below is a summary of key findings related to quality attributes as well as biological activities in relation to CD and UC:

Quality attributes:

A similar glycosylation profile with minor differences in afucosylated glycans (G0+Man5), which results in a lower binding affinity to FcγRIIIa and a lower activity in the most sensitive ADCC assay using NK cells as effector cells and tmTNFα Jurkat target cells was observed for CT-P13. The impact of the lower level of afucosylated glycans in CT-P13 has been comprehensively investigated:

1. The 3-way study confirmed that there was no difference in binding to FcγRI, FcγRIIa, FcγRIIb and FcRn, C1q binding (enzyme-linked immunosorbent assay - ELISA) and complement-dependent cytotoxicity (CDC) activity due to differences in core afucosylation levels.
2. The impact on Fc functionality is limited to a slight reduction in relative binding affinity of CT-P13 to recombinant FcγRIIIa (V and F hemizygote).
3. The slight difference in afucosylated glycans CT-P13 does not have discernible impact on immunogenicity following repeated administration using the sensitive assay applied in the clinical study program.

Biologic activity:
In addition, approximately 20 different orthogonal biological tests directly related to the mechanisms of action or downstream therapeutic effects were performed which compared CT-P13 to both EU and US approved REMICADE® and demonstrated:

- Highly similar binding affinity to sTNFα, neutralization of sTNFα, suppression of cytokine induction by sTNFα and suppression of apoptosis by sTNFα
- Similar binding affinity to tmTNFα, and resulting cytokine suppression through reverse signaling following binding to tmTNFα have been observed for CT-P13 versus EU and US approved REMICADE®. The induction of apoptosis through reverse signaling has been shown to be similar.
- Highly similar in induction of regulatory macrophages, suppression of T-cell proliferation and in mediating wound healing
- Highly similar FcγRIa, FcγRIIa, FcγRn and C1q binding affinity and CDC activity
- Slight differences in binding affinity to the FcγRIIIa and FcγRIIIb receptor observed for CT-P13 in comparison with REMICADE® were observed. The relevance of this finding was previously investigated using further models and it was demonstrated that the difference was not clinically meaningful. The findings are also supported by data from the literature.
- Marginal differences in ADCC activity using one artificial cell system were shown to have no clinically meaningful effect, since using more clinically relevant models and a similar assay system with cells derived from donors, high similarity was demonstrated. In common with other anti-TNF monoclonals, infliximab does not induce discernible ADCC activity against naturally derived target cells. Thus, ADCC does not appear to play a role in mediating therapeutic effect.

In conclusion, these comprehensive analyses have shown that CT-P13 is similar to EU and US approved REMICADE® in primary structure, higher order structure, aggregate and monomeric purity, and post-translational modifications. The differences detected by these highly sensitive methods have been shown to be of no clinical relevance in AS and RA studies and highly unlikely to have a clinically meaningful impact on efficacy or safety in IBD indications. The extensive ranges of *in vitro* and *ex vivo* biological assays have demonstrated comparable biological activities for CT-P13 and EU and US approved REMICADE® in assays mimicking the putative mechanisms of action of infliximab in CD and UC.

A brief overview of the tests and conclusions for the oligosaccharide profiling and biologic activity comparison between CT-P13 and REMICADE® are presented in Table 1 of Appendix 1.

4.2 Key Clinical Studies

Please note that the approval of INFLECTRA® for the IBD indications from both Health Canada and the CDR rely on the concept of extrapolation (see Section 6 for further explanation). Therefore, based on the already established high degree of similarity between INFLECTRA® and REMICADE®, post marketing studies (study reports) will be used to evaluate the clinical safety and efficacy of INFLECTRA® in CD and UC patients.

4.2.1 Post-Marketing Surveillance of CT-P13 100 mg (Infliximab) (monoclonal antibody, recombinant) to Evaluate its Safety and Efficacy in Korea

Study Name	Design	Objectives	Population
Post-Marketing Surveillance of CT-P13 100 mg (Infliximab) (monoclonal antibody, recombinant) to Evaluate its Safety and Efficacy in Korea. Referred to in remainder of document as study CT-P13 PMS	Phase 4 open-label safety surveillance study	The objectives of this PMS was to evaluate the safety and efficacy of CT-P13 in Korea under routine care.	• Adult patients with moderate to severe active CD who had not responded despite a full and adequate course of therapy with corticosteroid and/or and immunosuppressant; or who were intolerant to or had medical contraindications for such therapies. • Adult patients with FCD who did not show any response to general treatments (including antibiotics, drainage and immunosuppressive therapy). • Adult patients with moderate to severe active UC who had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine or azathioprine, or who were intolerant to or had medical contraindications for such therapies.

a) Study Characteristics

Brief description of the study

This PMS is an ongoing, open-label, single-arm, phase 4 study that is designed to evaluate the safety and efficacy of CT-P13 in all approved indications in South Korea. This surveillance is planned to be carried out in approximately 60 study centers in South Korea with an approximate sample size of 1,600 patients. An interim analysis was performed to evaluate safety and efficacy of CT-P13 in the specific IBD patient population. This interim analysis included 173 patients with IBD that have been treated with CT-P13 across 15 participating IBD clinical study centers. IBD patients enrolled in this study were either naïve to infliximab (N=113) or were previously treated with REMICADE® (N=60). Patient disposition, demographic and baseline characteristics are detailed below. IBD patients enrolled in this study could have been either naïve to infliximab or were previously treated with REMICADE®. There is no specified dosing window, as PMS is an observational study. Patients will be treated according to the product label and will be followed-up up to and including Week 30. Efficacy evaluations were performed according to planned visits and criteria set for each individual indication: FCD, UC and CD. All Adverse Events (AEs) and Serious Adverse Events (SAEs) which occurred during or after CT-P13 exposure were collected throughout the study.

Characteristics		Details for *(provide study name)*
Study Design	**Objective**	To evaluate the safety and efficacy of CT-P13 in Korea under routine care.
	Study period	Initiation Date:23 January 2013 Completion Date: on-going Cut-off date for this report: 14 November 2014
	Study centres	This study was conducted at 15 clinical centers in Korea.
	Design	Observational Phase 4 study, open label, single arm
	Inclusion criteria	Adults patients with moderate to severe CD, FCD and UC
	Exclusion criteria	N/A
Drugs	**Intervention**	N/A
	Comparator(s)	N/A
Duration	**Run-in**	N/A
	Treatment	N/A as this is an on-going Post Marketing Surveillance Study
	Follow-up	For FCD and moderate to severe active UC, the efficacy evaluation was performed at baseline, Week 14 and Week 30. The evaluation of efficacy in cases with moderate to severe active CD was performed at baseline, Week 2 and Week 30. All AEs and SAEs which occurred during and after CT-P13 exposure were collected throughout the study.
Outcomes	**Primary End Point(s)**	N/A
	Other End Points	• Clinical response for CD and UC • Clinical remission for CD and UC • Disease control for CD and UC • Rescue medication for CD and UC • Mucosal healing for UC
Notes	**Publications**	• Park SH, Kim YH, Lee JH *et al*. *Expert Rev Gastroenterol Hepatol*. 2015:9:sup1, 35-44 [1]. • clinicaltrials.gov identification code (e.g., NCTXXXXXXXX) : N/A

b) Intervention and Comparators

Dosing and Administration

Dose and regimen including dose escalation were complied with the approved posology by Korean Ministry of Food and Drug Safety and time intervals between doses were controlled flexibly upon the investigator's decision under routine care. Please refer to the CT-P13 Korean label for dosing and administration [2] . Patients will be treated with CT-P13 every 8 weeks (± 5 days) following induction therapy. For FCD and moderate to severe active UC, the efficacy evaluation was performed at baseline, Week 14 and Week 30. The evaluation of efficacy in cases with moderate to severe active CD was performed at baseline, Week 2 and Week 30. All AEs and SAEs which occurred during and after CT-P13 exposure were collected throughout the study.

Reference Product used in the Trial: N/A

Placebos and Controls (if applicable): N/A

Concomitant Medications
Any new treatments (i.e., treatments not ongoing at study entry) and dose increase for existing medications were considered as rescue treatments.
Concomitant medications for other medical conditions were permitted as clinically indicated subject to specific protocol requirements outlined below.

Permitted medications included the following:
- Paracetamol
- Oral 5-Aminosalicylic Acid (5-ASA) treatment
- Inhaled or topical dermatological (not per rectum) corticosteroids
- Systemic corticosteroids (e.g., prednisone, budesonide, cortisone acetate)
- Oral 5-ASA treatment in patients not receiving this medication at study entry. For patients receiving 5-ASA at study entry, no increase in dosage was allowed.
- Corticosteroids or 5-ASAs per rectum
- Other treatments for UC, either systemic or topical, initiated during the treatment or observation period
- Antibiotics used for treatment of IBD. These included, but were not exclusive to, agents in the quinolone class and metronidazole.

c) Outcomes (Key Efficacy and Safety Outcomes)
Efficacy evaluations are to be performed according to planned visits and criteria set for each individual indication. All efficacy evaluations are described below by indication:

Patients with FCD:
- Proportion of patients achieving clinical response defined as a reduction of at least 50% from baseline in the number of draining fistulas [3].
- Proportion of patients achieving clinical remission defined as the absence of draining fistulas [3].
- Proportion of patients with disease control defined by the exclusion of loss of response cases from disease control. Loss of response is defined by the recrudescence of draining fistulas, the need for a change in medication for CD or the need for additional therapy for persistent or worsening luminal disease activity, the need for a surgical procedure for CD, or the discontinuation of the study medication owing to a perceived lack of efficacy [3].

Patients with Moderate to Severe Active CD:
- Proportion of patients achieving clinical response defined by a ≥25% and ≥70 points decrease in Clinical Disease Activity Index (CDAI) score from baseline scores [4].
- Proportion of patents achieving clinical remission defined by CDAI score of <150 [4].
- Proportion of patients with disease control defined by the exclusion of disease worsening cases from disease control. Disease worsening is defined by an increase in CDAI of at least 70 points from the qualifying score with a total score of at least 175 and an increase in CDAI of 35% or more from the baseline value, or the introduction of a new treatment for active CD [4].

Patients with Moderate to Severe Active UC:

- Proportion of patients achieving clinical response defined by a decrease in partial Mayo scores from baseline of at least 2 points and at least 30%, with an accompanying decrease in the sub score for rectal bleeding of at least 1 point, or an absolute sub score for rectal bleeding of 0 or 1 [5].
- Proportion of patients achieving clinical remission, which is defined as a total partial Mayo score of 2 points or lower, with no individual sub score exceeding 1 point [6].
- Proportion of patients achieving mucosal healing defined by Mayo endoscopic sub score of ≤ 1 point.
- Proportion of patients with disease control defined that disease worsening case is excluded from disease control. Disease worsening is defined by an increase in partial Mayo score of ≥3 points from baseline (=before switching) value and a partial Mayo score ≥5 points.

Patients with Moderate to Severe Active CD and UC:

- For all IBD patients, proportion of patients receiving rescue medication was assessed. Rescue medication is defined as any concomitant medication that were commenced after the first infusion date to treat new or unresolved symptoms of CD or UC [7] [8].

The safety endpoints were:

- Serious adverse events (SAEs). SAE was considered as such if it:
  - resulted in death or life-threatening;
  - required inpatient hospitalization or prolongation of existing hospitalization;
  - caused a persistent or significant disability/incapacity;
  - resulted in a congenital anomaly/birth defect; or
  - associated with any other medically important condition.
- Adverse events (AEs)
- Other information about safety

Adverse events were coded using the Medical Dictionary for Regulatory Activities Version 16.0.

d) Statistical Analyses

- All statistical analyses were conducted using SAS Version 9.3 (SAS Institute, Inc.). Continuous data were summarized using descriptive statistics: n, mean, standard deviation, median, minimum and maximum, unless otherwise indicated. Categorical data were summarized using counts and percentages. Data presented in listings were sorted by indication and then by patient number and visit, where applicable. All analyses were performed by subgroup (Naïve, Switch): Naïve group consists of patients who had not received at least one dose of REMICADE® before first infusion of CT-P13.
- Switch group consists of patients who had ever received at least one dose of REMICADE® before first infusion of CT-P13.

Premedication

The premedication was summarized by indication, drug class and preferred term for the safety population. The premedication was qualified when corticosteroids, antihistamines or analgesics were commenced at CT-P13 infusion date for the purpose of prophylaxis. A frequency table for the maximum amount of dose received (mg/kg) is presented by indication for patients in the safety analysis set. Please refer to PMS study report, Table 9-4 [9, Table 9-4] showing the number and percentage of patients within each category of amount of dose received at each visit

Efficacy analysis

The efficacy analysis set consisted of all patients who received at least one dose of CT-P13 and had at least one assessment following baseline. Efficacy analyses were performed on the efficacy analysis set by applying different criteria for each indication. The proportion of patients achieving clinical response, remission and disease control were analyzed by indication. Descriptive statistics for actual value and change from Baseline were presented by indication and visit for number of fistulas, CDAI and Mayo score. LOCF method was considered for missing data imputation for clinical response and remission for naïve CD and UC patients. The proportion of patients achieving mucosal healing was analyzed in UC patients. The rescue therapy will be summarized by indication, drug class and preferred term for the safety population. The rescue therapy was qualified when any concomitant medication were commenced after the first infusion date to treat new or unresolved symptoms of CD or UC. Discontinued patients were not included in the summary tables for efficacy analysis at each visit.

Safety analysis

The safety analysis set consisted of all patients who receive at least one dose (full or partial) of the study treatment during any dosing period. All analyses of safety were conducted using the safety analysis set. Safety analyses were performed by presenting data on Treatment-Emergent Adverse Events (TEAEs), and duration of REMICADE® and CT-P13 administration. TEAEs were summarized by relationship, intensity, system organ class, and preferred term displaying the number and percentage of patients with at least one AE using only the worst intensity recorded at each level of summarization. The total number of events and number of patients with at least one AE overall system organ classes was also displayed. Adverse events were coded using the Medical Dictionary for Regulatory Activities Version 16.0. Rescue therapy and premedication were coded using the WHO Drug Dictionary Version 01 September 2013.

Analysis Sets

TABLE 1: NUMBER OF IBD PATIENTS IN EACH POPULATION - CT-P13 PMS STUDY

Analysis set	Moderate to severe active CD		Fistulising active CD		Moderate to severe active UC		Total		Total
	Naïve	Switched	Naïve	Switched	Naïve	Switched	Naïve	Switched	
Safety analysis set [1]	43	40	8	4	62	16	113	60	173
Efficacy analysis set [2]	39	31	6	4	54	11	99	46	145

Source: [10, Table 1]

[1] Patients administered at least 1 dose of CT-P13

[2] Patients administered at least 1 dose of CT-P13 and had at least one of assessment after treatment

For the description of the statistics protocol, please refer to the Clinical Trial Study Report [9, page 8].

e) Results

Baseline Characteristics

TABLE 2: SUMMARY OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS FOR (CT-P13 PMS STUDY SAFETY ANALYSIS SET IN TREATMENT-NAÏVE PATIENTS)

Parameter	Moderate to severe active CD (N=43)	Fistulising active CD (N=8)	Moderate to severe active UC (N=62)	Total (N=113)
Age (years)	31.8 (10.88)	27.9 (10.13)	45.2 (14.57)	38.9 (14.71)
Mean (SD)				
Median (range)	30.0 (18-67)	25.5 (18-48)	46.5 (19-74)	39.0 (18-74)
Sex, no (%)	34 (79.1)	6 (75.0)	40 (64.5)	80 (70.8)
Male				
Female	9 (20.9)	2 (25.0)	22 (35.5)	33 (29.2)
Body weight (kg)	57.1 (12.13)	71.2 (11.77)	58.5 (9.67)	58.8 (11.26)
Mean (SD)				
Median (range)	54.8 (35-80)	67.9 (57-93)	58.2 (40-81)	58.0 (35-93)
Baseline disease activity[1]	340.0 (90.35)	1.6 (0.92)	6.8 (1.13)	n/a
Mean (SD)				
Median (range)	340.6 (181-564)	1.0 (1-3)	7.0 (3-9)	

Source: [10, Table 2] [1]CDAI for moderate to severe active CD, No. of fistula for fistulising active CD and partial Mayo scoring system (MSS) in moderate to severe active UC patients were used to assess disease activity.

TABLE 3: SUMMARY OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS FOR (CT-P13 PMS STUDY SAFETY ANALYSIS SET IN SWITCHED PATIENTS)

Parameter	Moderate to severe active CD (N=40)	Fistulising active CD (N=4)	Moderate to severe active UC (N=16)	Total (N=60)
Age (years)	31.1 (10.41)	33.0 (13.34)	42.9 (13.54)	34.3 (12.43)
Mean (SD)				
Median (range)	28.5 (19-60)	33.5 (20-45)	41.0 (21-64)	30.0 (19-64)
Sex, no (%)	24 (60.0)	3 (75.0)	9 (56.3)	36 (60.0)
Male				
Female	16 (40.0)	1 (25.0)	7 (43.8)	24 (40.0)
Body weight (kg)	58.9 (13.45)	64.4 (12.36)	58.0 (9.46)	59.0 (12.34)
Mean (SD)				
Median (range)	60.0 (37-97)	64.3 (50-79)	56.9 (40-73)	59.0 (37-97)
Baseline disease activity[1]	168.9 (112.65)	0.5 (0.58)	4.8 (2.81)	n/a
Mean (SD)				
Median (range)	134.0 (24-412)	0.5 (0-1)	4.5 (0-9)	

Source: [10, Table 3] [1]DAI for moderate to severe active CD, No. of fistular for fistulising active CD and partial MSS in moderate to severe active UC patients used to assess disease activity.

The demographic and baseline characteristics of patients were in line with target patient population in CT-P13 and REMICADE® label. Overall, there were no important differences between CD and UC patients except that UC patients were slightly older than CD patients. There was greater proportion of males compared to females in CD and UC subgroups. Baseline disease characteristics in all subgroups were in line with moderate-to-severe active status of the disease. The majority of infliximab-naïve patients were exposed to at least 3 doses of treatment which spanned 6 week induction period with 52.2% of patients reaching dose 6 (30 weeks). Likewise, the majority of switched patients were exposed to at least 3 doses of treatment and 65.0% of patients reached dose 5.

Concomitant Conditions and Medications

A total of 48 of 173 (27.7%) patients required rescue medication to control IBD symptoms. However, less than 15% of CD and UC patients required rescue anti-inflammatory, corticosteroids or immunosuppression agents. Overall, the proportion of use of rescue medication was higher in infliximab-naïve groups compared to switched groups [9, page 10].

Efficacy Results

The study was not powered for efficacy but had a positive outcome for the efficacy endpoint of induction and maintenance of response in CD, FCD and UC patients regardless of treatment-naïve or switch status. Please see below key efficacy results.[2,3]

(A) The following results are based on complete case analysis:

(i) Among CD infliximab-naïve patients, [redacted] and [redacted] achieved clinical response and [redacted] and [redacted] achieved clinical remission at week 14 and 30, respectively.

(ii) Among FCD infliximab-naïve patients, [redacted] and [redacted] achieved clinical response at week 14 and 30, respectively. [redacted] and [redacted] achieved clinical remission at week 14 and 30, respectively. [redacted].

(iii) Among FCD patients switched from REMICADE® to CT-P13, clinical remission and disease control was [redacted]

(iv) Among UC infliximab-naïve patients, [redacted] and [redacted] achieved clinical response and [redacted] and [redacted] achieved clinical remission at week 14 and 30, respectively.

(v) [redacted] and [redacted] UC infliximab-naïve patients experienced mucosal healing at week 14 and 30 while [redacted] patients who were switched from REMICADE® to CT-P13 experienced mucosal healing throughout visits 2-5.

(B) The following results are based on imputation of missing data with LOCF and include all patients in the efficacy analysis set. The need for rescue medication includes all patients in safety analysis set:

(i) Among CD infliximab-naïve patients, 34/39 (87.2%) and 31/39 (79.5%) achieved clinical response at week 14 and 30, respectively. 27/39 (69.2%) and 23/39 (59.0%) achieved clinical remission at week 14 and 30, respectively. Rescue medication was needed by 7/43 (16.3).

(ii) Among CD patients who were switched from REMICADE® to CT-P13, 25/31 (80.6%) achieved remission throughout visits 2-6 and 27/31 (87.1%) patients did not experience disease worsening. Rescue medication was needed by 9/40 (22.5%).

(iii) Among UC infliximab-naïve patients, 40/53 (75.5%) and 39/54 (72.2%) achieved clinical response at week 14 and 30, respectively. 26/53 (49.1%) and 20/54 (37.0%) achieved clinical remission at week 14 and 30, respectively. Rescue medication was needed by 30/62 (48.4%).

(iv) Among UC patients who were switched from REMICADE® to CT-P13, 5/11 (45.5%) achieved remission throughout visits 2-5 and no patients experienced disease worsening. Rescue medication was needed by 2/16 (12.5%).

Safety Results

Safety assessments were carried out during and after CT-P13 exposure and events were recorded if they occurred at any time during the study period.[2,3]

Overall, CT-P13 was well-tolerated in all treated patients. 51 TEAE were reported in 38 patients (22.0%). In patients with CD, 19 events occurred in 15/83 patients (18.1%), in FCD 2 events occurred in 2/12 patients (16.7%), and in UC 30 events occurred in 21/78 patients (26.9%). 22 events were considered to be related to treatment in 18 patients. Most events were of mild severity in 25 patients. Five TESAEs were reported in 5 (2.9%) patients: moderate treatment-related tuberculosis (improved), moderate treatment-related lung abscess (resolved), moderate treatment-related anaphylactic reaction (resolved), severe treatment-related IRR (resolved), and severe treatment-unrelated abdominal pain (resolved). Among these 5 TESAEs, a total of 4 cases were considered to be related to treatment and 3 cases led to discontinuation from the study (IRR, lung abscess, and anaphylactic reaction). Infection and serious infection were reported in 9 patients (5.2%, [redacted]) and 2 patients (1.2%), respectively. Only one patient (0.6%) had active tuberculosis after CT-P13 exposure. Infusion-related reaction including hypersensitivity and anaphylaxis was reported in 9 patients (5.2%). There were no patients with malignancy, pneumonia, death or any other events of special interest reported in the study.

Dose escalation results

- The majority of patients (59.0%) received doses of 5 mg/kg of CT-P13. 41.0% patients were treated with doses >5 -≤10 mg/kg. There were no notable differences in dose-escalation between infliximab-naïve and switched patients.

There were no notable differences in incidence of TEAEs between infliximab-naïve and switched patients with 23.9% and 18.3% of patients, respectively, reported TEAEs. Furthermore, there were no notable dose-dependent differences in distribution of TEAEs between patients who received 5 mg/kg or >5 mg/kg doses of CT-P13 [9, page 10].

4.2.2 Other Lines of Evidence for Use of CT-P13 in IBD

a) Other Ongoing Studies Sponsored by Celltrion

(i) CT-P13 3.4: This is a phase III efficacy and safety study to demonstrate non-inferiority of CT-P13 with Remicade in adults with active CD over 54 weeks. The design is randomized, double-blind, parallel group. An enrollment of 214 patients is planned. In an interim analysis (week 14), formation of ADA was

found to be similar between CT-P13 and US-licensed Remicade in patients receiving 5 mg/kg [75, page 65].

(ii) CT-P13 4.3: This is a phase IV, observational registry study in the European Union and South Korea to evaluate the efficacy and safety of CT-P13 in patients with CD or UC over a 5 year period. An enrollment of 500 patients is planned. No results are available to date.

b) Non-Celltrion Sponsored Studies

The manufacturer conducted a systematic search to identify non-Celltrion sponsored studies that evaluated the use of CT-P13 in IBD. Six observational studies in adult patients were identified. These studies were conducted in Norway[4], Hungary[5,6], the Czech Republic [7], and Korea.[8,9] Each study is summarized briefly and selected results provided.

Norway[4]: A prospective, observational study was conducted in a single center in 46 patients with CD and 32 patients with UC. Patients received three induction doses of CT-P13 at weeks 0, 2, and 6, with the majority receiving 5 mg/kg. Efficacy and safety were assessed up to week 14. Of the patients with CD, 79% achieved remission (Harvey-Bradshaw Index score ≤4) and of the patients with UC, 56% achieved remission (partial Mayo score ≤2). Statistically significant reductions in C-reactive protein and calprotectin from baseline to week 14 were observed. Adverse effects included IRRs (1 patient with CD and 1 with UC), colectomy (1 patient with UC), muscle and joint pain due to antibody formation (1 patient with CD), and infections (patients with CD: infectious enterocolitis, herpes zoster, herpes simplex, recurrent upper airway infection; patients with UC: pneumonia and erysipelas).

Hungary[5,6]: Gecse et al. conducted a nationwide, multicentre prospective observational study to assess the efficacy, safety, and immunogenicity of CT-P13 in patients with CD (N=126) or UC (N=84). Patients received CT-P13 5 mg/kg induction at weeks 0, 2, and 6 and then every 8 weeks thereafter. Clinical response was achieved by 81.4% of patients with CD (decrease in CDAI >70 or at least 50% reduction in the number of draining fistulas) and 77.6% of patients with UC (decrease in partial Mayo score >3) at week 14. Clinical remission was achieved by 53.6% of patients with CD (CDAI <150 or no fistula drainage) and 58.6% of patients with UC (partial Mayo score < 3). Significantly more patients who were infliximab-naïve achieved clinical remission at week 14 compared with patients who had previously received the innovator product. Infusion-related reactions were experienced in 14 (6.6%) patients and infections in 12 (5.7%). Infusion-related reactions occurred at a higher incidence in patients who were switched from innovator product (27% vs. 2.5%). Molnar et al. examined mucosal healing subsequent to CT-P13 administration in 12 patients with UC. At week 6, clinical response was obtained by 2 patients, clinical remission by 5 patients, and mucosal healing was observed in 7 patients.

The Czech Republic[7]: A post-market surveillance study of 140 patients with IBD (107 CD and 33 UC) was conducted with an interim analysis of efficacy and safety at week 10 (complete follow-up will be to week 30). Of the 140 patients, 36 were treatment-naïve and 104 were switched to CT-P13 from other biological agents. Efficacy data were available for treatment-naïve patients only (23 CD and 13 UC). Statistically significant reductions in Harvey-Bradshaw Index for CD and Simple Clinical Colitis Activity Score (SCCAI) for UC from baseline to week 10 were observed. Clinical response was obtained by 5 patients (21.7%) with CD (decrease in Harvey-Bradshaw Index ≥3) and 6 (46.2%) patients with UC (decrease in SCCAI ≤2). Clinical remission was obtained by 17 (73.9%) patients with CD (Harvey-Bradshaw Index ≤4) and 2 (15.4%) patients with UC (SCCAI ≤2). Compared with baseline, there were statistically significant reductions in C-reactive protein and fecal calprotectin in both CD and UC. Six

TEAEs (IRRs, pneumonia, C.difficile infection, tonsillitis, and dermatitis psoriasiform) were experienced by 6 (4.3%) patients (3 CD and 3 UC).

Korea[8,9]: Kang et al. evaluated 17 patients with IBD (8 CD and 9 UC) who received CT-P13 at a single study center. Among treatment-naïve patients (N=8), clinical response (CD: decrease CDAI >60; UC: decrease >30% in the activity index + decrease in rectal bleeding and endoscopy subscores) and remission (CD: CDAI <150; UC: Mayo score ≤2 and no subscores >1) were achieved in 7 (2 CD and 5 UC) at week 8. Among patients who switched to CT-P13 from innovator product (N=9), 8 had similar clinical outcomes. One patient with CD had loss of response. Jung et al. conducted a retrospective multicenter study in patients with CD (N=59) and UC (N=51) with follow-up to 54 weeks. At week 8, clinical response and remission in treatment-naïve patients with CD (N=32) were 90.6% and 84.4% respectively. At week 54, clinical response occurred in 7/8 (87.5%) and remission in 6/8 (75.0%). In treatment-naïve patients with UC (N=42), clinical response and remission at week 8 were 81.0% and 38.1% respectively. At week 54, clinical response occurred in 12/12 (100%) and remission in 6/12 (50%). Mucosal healing in UC was achieved in 14/24 (58.3%) at week 8 and in 2/3 (66.7%) at week 54. Among patients who switched from the reference product (27 CD and 9 UC), efficacy was maintained in 25 (92.6%) with CD and 6 (66.7%) with UC. There were statistically significant declines in C-reactive protein and erythrocyte sedimentation rate in CD and UC. Six (11.8%) patients with UC experienced an AE.

4.2.3 Summary of Safety Section

a) Safety Evaluation Plan

The objective of the clinical development program for CT-P13 was to demonstrate that CT-P13 is comparable to the reference medicinal product, REMICADE®, in terms of its clinical pharmacology, efficacy and safety. Data from clinical trials in RA and AS patients showed that the safety profiles of CT-P13 and REMICADE® were similar. In view of these data and the structural, biological, toxicological and pharmacokinetic (PK) comparability to the reference drug product REMICADE® (CTD Modules 3.2R and 2.4), CT-P13 is also expected to display a comparable safety profile in CD and UC patients. Therefore, the safety evaluation in CD and UC patients was based on the safety profile of REMICADE® as presented in the product information from REMICADE® product monograph [11] and the Summary of Product characteristics [12].

To compare the safety data of CT-P13 and that of REMICADE®, literature searches have been performed to identify articles reporting REMICADE® studies. The data from these historical studies were included in the meta-analyses with regard to the incidence of Adverse Event of Special Interest (AESI), in particular to the incidence of (see CTD Module 2.7.4.2.1.5):

- Infections including serious infections, pneumonia, active tuberculosis
- Infusion-related reactions including anaphylactic reactions
- Malignancies including lymphoma

The literature searches focused on RCTs and also considered observational studies. Publications were selected when they reported the methodology of collecting safety data and specifically AEs and when the incidence of AEs was clearly captured and reported using reliable denominators. For further details, refer to a Systematic Literature Review on the Safety of infliximab in the treatment of patients with CD and UC [13] and a Systematic literature review report on REMICADE® observational studies [14]. Below are comparisons of overall rates (per 100 patient-years with 95% confidence intervals) from RCTs of Remicade (ACCENT I, ACCENT II, and SONIC, + others), observational studies of Remicade, and observational studies of CT-P13.[10]

1. Infusion-related reactions:
CD: Remicade (RCTs) – [redacted] per 100 patient-years
Remicade (observational) - [redacted] per 100 patient-years
CT-P13 (PMS + non-Celltrion sponsored studies) – [redacted] per 100 patient-years
UC: Remicade (RCTs) – [redacted] per 100 patient-years
Remicade (observational) – [redacted] per 100 patient-years
CT-P13 (PMS + non-Celltrion sponsored studies) – [redacted] per 100 patient years

2. Infections:
CD: Remicade (RCTs) – [redacted] per 100 patient-years
Remicade (observational) - [redacted] per 100 patient-years
CT-P13 (PMS + non-Celltrion sponsored studies) – [redacted] per 100 patient-years
UC: Remicade (RCTs) – [redacted] per 100 patient-years
Remicade (observational) – [redacted] per 100 patient-years
CT-P13 (PMS + non-Celltrion sponsored studies) – [redacted] per 100 patient years

3. Pneumonia:
CD: Remicade (RCTs) – [redacted] per 100 patient-years*
Remicade (observational) – [redacted] per 100 patient-years
CT-P13 (PMS + non-Celltrion sponsored studies) – [redacted] per 100 patient-years
UC: Remicade (RCTs) – [redacted] per 100 patient-years
Remicade (observational) – [redacted] per 100 patient-years
CT-P13 (PMS + non-Celltrion sponsored studies) – [redacted] per 100 patient-years
* *Pneumonia was not reported in ACCENT I, ACCENT II, or SONIC*

4. Tuberculosis:
CD: Remicade (RCTs) – [redacted] per 100 patient-years
Remicade (observational) – [redacted] per 100 patient-years
CT-P13 (PMS + non-Celltrion sponsored studies) – [redacted] per 100 patient-years
UC: Remicade (RCTs) – [redacted] per 100 patient-years
Remicade (observational) – [redacted] per 100 patient years
CT-P13 (PMS + non-Celltrion sponsored studies) – [redacted] per 100 patient-years

5. Malignancies:
CD: Remicade (RCTs) – [redacted] per 100 patient-years
Remicade (observational) – [redacted] per 100 patient-years
CT-P13 (PMS + non-Celltrion sponsored studies) – [redacted] per 100 patient-years
UC: Remicade (RCTs) – [redacted] per 100 patient-years
Remicade (observational) – [redacted] per 100 patient-years
CT-P13 (PMS + non-Celltrion sponsored studies) – [redacted] per 100-patient-years

6. Surgery:
CD: Remicade (RCTs) – [redacted] per 100 patient-years*
Remicade (observational) – [redacted] per 100 patient-years
CT-P13 (PMS + non-Celltrion sponsored studies) – [redacted] per 100 patient-years
UC: Remicade (RCTs) – [redacted] per 100 patient-years*
Remicade (observational) – [redacted] per 100 patient-years
CT-P13 (PMS + non-Celltrion sponsored studies) – [redacted] per 100-patient-years
* *Data from the major RCTs of Remicade + other RCTs*

7. Disease-Related Hospitalization:
CD: Remicade (RCT) – [redacted] per 100 patient-years
Remicade (observational) – [redacted]
CT-P13 (PMS + non-Celltrion sponsored studies) – [redacted] per 100 patient-years
UC: Remicade (RCT) – [redacted] per 100 patient-years
Remicade (observational) – [redacted]
CT-P13 (PMS + non-Celltrion sponsored studies) – [redacted] per 100-patient-years

In addition, safety data was collected from several post-marketing observational studies. The safety population and outcomes are further described in the sections below. For additional information on the specific studies please refer to the Clinical Study Reports (CSRs) included in the listed references.

b) Safety Populations Evaluated

The safety database of CT-P13 consists of data from the 2 ongoing clinical trials conducted with CT-P13 for CD and UC: the Phase 4 trial CT-P13 4.1 in IBD patients [15], and the observational Phase 4 trial CT-P13 PMS [9]. The latter study is described in detail in Section 4.2. CT-P13 4.1 is a small (N=20) phase IV, ongoing (four year), open-label, single arm study conducted in adult patients with CD or UC in South Korea.[11] An interim analysis of efficacy and safety in 10 patients ([redacted]) from [redacted] study centers has been presented. [redacted]. Analyses of the safety of CT-P13 at doses >5 mg/kg included data from Study CT-P13 PMS and Study B2P13111, which is an Extension Study of the Phase I/II Clinical Study of CT-P13 in Treatment of Patients with Rheumatoid Arthritis [16].

For Study CT-P13 PMS [redacted], the safety analysis set consisted of all patients who received at least one dose (full or partial) of the study treatment during any dosing period. A total of 173 IBD patients have been treated with CT-P13 in Study CT-P13 PMS and 75 patients were treated with doses >5 mg/kg. In Study B2P13111, [redacted]. A total of 71 RA patients were treated with CT-P13. [redacted].

c) Overview of Safety

The safety database of CT-P13 in IBD patients has been specially evaluated with regard to the identified and potential risks of REMICADE® i.e., IRRs, infections, in particular pneumonia and tuberculosis, and malignancies. In addition, analyses on events of surgery or disease-related hospitalization have been performed. The results of these analyses are presented in the following sections. In addition, the findings on IRRs, infections, pneumonia, tuberculosis and malignancies from RCTs conducted with REMICADE® as well as from observational studies are summarized and compared with the safety data from Study CT-P13 PMS, Study CT-P13 4.1, and non-CELLTRION sponsored studies.

d) Treatment Emergent Adverse Events (TEAS)

Study CT-P13 PMS (Interim CSR)

A total of 51 TEAEs were reported in 38 patients (22.0%). Of these, 22 events were considered to be related to treatment in 18 patients. There was no notable difference in incidence of TEAEs between infliximab-naïve and switched patients with 23.9% and 18.3% of patients reporting TEAEs, respectively. More TEAEs were reported by UC patients compared to CD patients; 30 TEAEs by UC patients and 19 TEAEs by CD patients. Patients with FCD reported 2 TEAEs. The most frequently (≥5 patients) reported system organ classes (SOCs) included infections and infestations (9 patients), skin and subcutaneous

tissue disorders (8 patients), gastrointestinal (GI) disorders (5 patients), general disorders and administration site conditions (5 patients). Most TEAEs were of mild severity (10 patients reported mild TEAEs considered related to treatment and 15 patients reported mild TEAEs considered to be unrelated to treatment); 7 patients reported related moderate TEAEs and also 7 patients reported unrelated moderate TEAEs. Two TEAEs were assessed to be of severe severity. Infections and GI disorders were the most frequently reported TEAEs, which is not inconsistent with the safety profile of REMICADE® in IBD patients.

Study CT-P13 4.1 (Interim CSR)

[redacted]

e) Deaths

No deaths were reported in the interim CSRs of Studies CT-P13 PMS, [redacted].

f) Treatment Emergent Serious Adverse Events (TESAEs)

Study CT-P13 PMS (Interim CSR)

Five TESAEs were reported by 5 (2.9%) patients in the study (CTD Module 2.5-12); of these, 4 were considered to be related and 1 to be unrelated to treatment. The TESAEs were reported by 4 patients receiving 5 mg/kg as maximum dose and 1 patient in the > 5 mg/kg - ≤ 7 mg/kg group. The TESAEs reported in the study are consistent with the safety profile of REMICADE® as described in the REMICADE® Product Monograph [11]. No unexpected TESAE occurred during the study.

Study CT-P13 4.1 (Interim CSR)

[redacted]

g) Reactions Due to Infusion of the Study Drugs

[redacted]. In Study CT-P13 PMS, a total of 10 IRRs were reported by 9 IBD (9 of 173; 5.2%) patients, [redacted]. In the CD group, 2 patients reported IRRs (both switched to CT-P13) and in the UC group 8 patients (6 infliximab-naïve, 2 switch). None of the patients with FCD reported IRRs. Four IRRs led to permanent discontinuation of treatment. The incidence of IRRs was not higher in the group of patients receiving doses of > 5 mg/kg (3 of 71, 4.2%) compared to patients receiving 5 mg/kg as maximum dose (6 of 102, 5.9%).

In Study CT-P13 4.1, 2 (20%) patients experienced IRRs; 1 patient experiencing vomiting (possible related, moderate) and nausea (possible related, moderate) in the CD group, 1 patient reporting skin exfoliation (possible, mild) and rash (probable / likely, mild) in the UC group. None of these IRRs led to discontinuation of treatment.

h) Infections

In Study CT-P13 PMS, a total of 10 TEAEs of infections were reported by 9 IBD patients; of these, 3 were considered to be related and 6 to be unrelated to treatment. The 3 TEAEs considered to be related included: 1 TEAE of tuberculosis (moderate) experienced by a FCD patient, 1 TEAE of rhinitis (mild) reported by a treatment-naïve UC patient, and 1 TEAE of lung abscess (moderate) reported by a treatment-switch UC patient. The event of rhinitis, however, was confirmed to be an IRR by the site investigator. TEAEs unrelated to treatment included folliculitis (mild), upper respiratory infections (3 mild, 2 moderate), and urinary tract infection (moderate). The incidence of infections was not higher in the group of patients receiving doses of > 5 mg/kg (2 of 71, 2.8%) compared to patients receiving 5 mg/kg as maximum dose (7 of 102, 6.9%).

[redacted]

Overall, 1 case of tuberculosis (Study CT-P13 PMS) was reported in IBD patients. For further details, refer to CTD Module 2.7.4.

i) Surgery

No cases of surgery were reported in the period covered by the PMS interim CSR.

j) Hospitalization (disease-related)

In Study CT-P13 PMS, 1 treatment-naïve patient with CD was hospitalized. No other cases of hospitalization were reported in the period covered by the interim CSR [17, Table 24].

k) Post-marketing Data

As previously mentioned, REMSIMA® and INFLECTRA® are the same molecule, the infliximab biosimilar (CT-P13) manufactured by Celltrion Healthcare Corporation, just marketed and distributed under different commercial names in different countries. As such, the post marketing data for CT-P13 is based on both the periodic benefit- risk evaluation report (PBRER) [18], dated 23Mar2015 for the REMSIMA® brand as well as the periodic safety update report (PSUR) dated 29Mar2016 for the INFLECTRA® brand [19]

REMSIMA® (infliximab; CT-P13)

This report contains safety data from individual case reports derived from post-marketing spontaneous reporting, published literature and clinical trials, covering the period from 20Jul2014 to 20Jan2015 (for further details, see CTD Module 2.7.4). [redacted]. During the reporting period, no new, ongoing, or closed signals were identified for infliximab. No new information was received for the previously identified or potential risks and there was no update on missing information during this reporting period. There were no actions taken or risk minimization activities proposed for any safety reason. Overall, no significant new safety information was identified from the review of worldwide safety data during the reporting period that would warrant changes to the Reference Safety Information of infliximab. The benefit-risk ratio of infliximab remains favorable.

This report summarizes the safety information received by the Product Safety Department of Hospira, for INFLECTRA® (infliximab), during the period 21Jul2015 to 20Jan2016 (for further details, see the PSUR document included in the listed references). Sources of adverse reporting data within this PSUR include spontaneous reports (medically confirmed and non-medically confirmed), reports from regulatory

authorities, reports from non-Hospira sponsored studies or named patient/compassionate use programs, and the literature. [redacted]. During the reporting period covered by this PSUR, there were no actions taken with INFLECTRA® (infliximab) for safety reasons, by either the Regulatory Authorities or, by Hospira as the MAH and no changes in the efficacy of INFLECTRA® (infliximab) were reported either. Following a review of the adverse event information received during the 6 month period covered by this report, the risk-benefit balance of INFLECTRA® (infliximab) is considered favorable

4.3 Pharmacokinetics

The PK similarity of REMICADE® and CT-P13 was demonstrated by a phase I (CT-P13 1.1) study in AS patients with 5 mg/kg and a phase III (CT-13 3.1) study in RA patients with 3 mg/kg. These studies were presented and described within the previous CDR submission for INFLECTRA®.

Dose proportionality of CT−P13 in the range of 3−10 mg/kg was analyzed in a PK modeling study to support IBD indication dosing regimen. The primary objective of this analysis was to evaluate the dose proportionality of CT−P13 based on the following: pharmacokinetic data from the phase I study, external validation with phase III data and review of previous pharmacokinetic studies on REMICADE®. Refer to the CT-P13 PK Modelling Report for further details [20]. This study has shown that there are no differences in pharmacokinetic parameters between REMICADE® and CT−P13. Both REMICADE® and CT−P13 appear to be dose proportional in the dose range of 3−5 mg/kg based on the external validation. The pharmacokinetic parameters of REMICADE® are known to be proportional to the doses given (5 and 10 mg/kg in patients with CD, 5, 10, and 20 mg/kg in patients with RA) in previous pharmacokinetics reports of REMICADE® and CT-P13 were linear (dose proportional exposure) in our studies as observed in previous reports. For further discussion on REMICADE® PK linearity, please refer to Appendix I.

In addition, several non-sponsored studies have investigated CT-P13 PK in IBD population. An overview of the data is provided below.

The Observational Hungarian Nationwide IBD Study [21, 22], that enrolled 90 CD patients and 51 UC patients as of February, 15, 2015, showed that for both CD and UC patients, trough levels increased from pre-dose status at week 0 to week 2 and subsequently stabilized between weeks 6 and 14. Preliminary results through induction therapy measured by week 14 showed therapeutically meaningful concentrations of drug present in patients. A similar study was done by the same group using REMICADE® [23]. The results in the current study for CT-P13 are comparable to those reported previously for REMICADE® [22]. A cohort study that is currently underway in Norway [24, 25] has enrolled 44 CD patients and 30 UC patients as of January, 31, 2015, including 56 patients who were naïve to infliximab therapy and 18 patients who were switched from REMICADE® to CT-P13. The mean trough levels at week 14 in CD patients was 7.0 mg/L (range: 0.0-21.8 mg/L), and for UC patients it was 6.1 mg/L (range: 0.0–16.7 mg/L)[25]. Another observational study from Prague in 140 IBD patients showed a median trough level of CT-P13 in all treatment-naïve patients of 14.8 µg/mL (0.9-45.0 µg/mL) and 8.7 µg/mL (0.2-45.0 µg/mL) at Weeks 2 and 6, respectively. The median trough level of CT-P13 in all switched patients were 2.4 (0-22.0 µg/mL) at baseline and 3.2 (0-19.0 µg/mL) at week 8 after the first infusion [26].

In conclusion, CT-P13 has demonstrated a linear and predictable pharmacokinetic profile that was highly similar to REMICADE® in modeling, sponsored and non-sponsored observational studies.

4.4 Immunogenicity

Immunogenicity data was thoroughly assessed in the key pivotal studies presented in the previous CDR submission (PLANETAS and PLANETRA Studies). The following section summarizes data relevant to CD and UC and briefly discusses immunogenicity similarity.

A series of studies were undertaken to investigate if immune reactivity against REMICADE® is cross-reactive with CT-P13. Sera from IBD patients who developed anti-infliximab (ATI) antibodies following treatment with REMICADE® were examined for cross-reactivity to CT-P13 by comparison of antibody titers using an ELISA assay [27, 28]. 52 sera obtained from 46 IBD patients and healthy individuals were tested. None of the patients was ever exposed to CT-P13. Testing was performed by a sensitive and validated anti-Lambda chain semi-quantitative ELISA. ATI detection for this assay is 2.7 µg/ml. When testing REMICADE® -sensitized IBD sera, there was strong correlation between titers of ATI reactive to EU-approved REMICADE® and titers of ATI cross-reactive with US approved REMICADE® and CT-P13 in patients never exposed to US approved REMICADE® or to CT-P13. These similar cross-reactivity results point to shared immuno-dominant epitopes on REMICADE® and CT-P13. Whilst these reassuring data were generated *in vitro*, they support the notion that the immunogenic potential of REMICADE® and CT-P13 and the characteristics of cross-reactivity with clinically relevant anti-drug antibodies (ADA) in IBD patients are similar and will translate into similar immunogenicity features in clinical settings.
Another cohort experience funded by the Norwegian Government is being conducted to accumulate experience with CT-P13 in Norway following product launch in January 2014. This Nor-Switch study is an ongoing randomized, double-blind, parallel group study with 500 patients across all indications [24]. [redacted]
In Hungary, a prospective, multicenter, observational cohort was designed to examine the safety and efficacy of CT-P13 in clinical response and the induction and maintenance of remission in CD and UC [29], [21]. [redacted]

TABLE 4: [redacted]

[redacted]				

The immunogenicity in terms of ADA positivity results obtained by CELLTRION from Studies CT-P13 1.1 and CT-P13 3.1 (which previously presented and described in the previous CDR Submission for INFLECTRA®) are in line with those reported in the literature indicating that the state of the art test methodology applied in CT-P13 studies provides results in line with those of the assays employed in the more recently reported studies. The use of concomitant MTX and other immunomodulatory therapies is known to differ between approved conditions. Nevertheless, it is evident that the AS and RA patient populations represent sensitive populations in which to compare immunogenicity of CT-P13 and REMICADE®. The immunogenicity in other populations (PsO, PsA, CD and UC) is not likely to differ from the levels observed in AS and RA patients since the use of MTX is either less common (PsO, CD and UC)

or optionally indicated (PsA) and therefore approximate to conditions tested in the CT-P13 clinical program.

Overall, the results of the immunogenicity assessment of the studies conducted with CT-P13 show that the proportion of patients developing ADAs while treated with CT-P13 is similar to that for those treated with REMICADE®.

5. CRITICAL APPRAISAL OF CLINICAL STUDIES

5.1 Internal Validity

Most clinical evidence currently available to evaluate the efficacy and safety of CT-P13 for CD or UC comes from observational studies (Celltrion-sponsored studies, non–Celltrion-sponsored studies, and post-marketing data). One RCT (CT-P13 3.4) compared CT-P13 with the reference product, Remicade, in adults with CD. The observational studies of CT-P13 in CD or UC are all single arm without direct comparisons with Remicade. Only naive indirect comparisons of safety end points and some efficacy end points with Remicade are available from the manufacturer's systematic review[10] and manufacturer-submitted data to Health Canada.{20} The absence of randomized trials in the clinical body of evidence for CT-P13 in bowel diseases makes it difficult to ascribe any observed improvements in efficacy, or any apparent maintenance of treatment effect, to the intervention. In addition, the degree of similarity in efficacy, safety, and immunogenicity between CT-P13 and Remicade have yet to be clearly delineated with experimental trials. In the discussion below, specific critical appraisal points are provided for the study CT-P13 PMS, as this was the key clinical study presented in the manufacturer's submission.

CT-P13 PMS is an ongoing (four year) phase IV, open-label, single arm study of CT-P13 for all approved indications in South Korea. An interim analysis was conducted in adults with moderately to severely active CD (N = 83), FCD (N = 12), and UC (N = 78) across 15 study centres in South Korea with follow-up of 30 weeks. Of the 173 patients, 113 were treatment-naive to infliximab and 60 were switched to CT-P13 from the reference product, Remicade. CT-P13 was administered every 8 weeks (± 5 days) after induction therapy of three 5 mg/kg doses at weeks 0, 2, and 6. Most patients (59.0%) received doses of 5 mg/kg. Higher doses of 5 mg/kg to 10 mg/kg were administered to 41% of patients with a flexible titration schedule. The majority of patients received at least three doses of treatment during a six week induction period (90.3% of treatment-naive and 86.7% of treatment- switch). Among treatment-naive and treatment-switch patients, 52.2% and 11.7% respectively reached dose 6 at week 30. The efficacy analysis set consisted of patients who received at least one dose of CT-P13 and had at least one assessment following baseline (N = 145, 83.8%). Missing data were imputed using LOCF. All patients were included in safety analyses. The manufacturer submitted data to Health Canada suggesting similar efficacy for clinical response and remission in CD and UC and mucosal healing in UC at weeks 14 and 30 between CT-P13 PMS and historical Remicade data.{20}

The internal validity of CT-P13 PMS is limited because of its non-comparative, open-label study design. The magnitude of improvement in efficacy outcomes due to CT-P13 administration in comparison with Remicade is unknown without a comparator group. Also, confounders, such as variations in symptoms over time and the effect of concomitant treatments, could not be adjusted for with a non-comparative study design. The absence of blinding may have influenced the assessment of subjective components of the scoring tools, such as severity of abdominal pain and general well-being of the CDAI and physician's global assessment of the Mayo score.

The sample size is relatively small, with a total of 83 patients with CD, 12 with FCD, and 78 with UC. When analyses were stratified according to treatment-naive or switch status, sample sizes became even smaller making it difficult to draw conclusions (e.g., in FCD, only 8 patients were treatment-naive and 4 patients treatment-switch). Patients who received at least one dose of CT-P13 but who did not have at least one post-baseline efficacy assessment (n = 28, 16.2%) were excluded from efficacy analyses. Of the

28 patients excluded from efficacy analyses, 8 discontinued treatment for the following reasons: lack of efficacy and switch to another treatment (n = 2), experience of an AE (n = 4), loss to follow-up (n = 1), and pregnancy (n = 1).[13] The complete case analyses showed that a considerable number of patients were not evaluated at follow-up visits (e.g., only 14/39 and 20/39 patients who were infliximab-naive with CD were evaluated at weeks 14 and 30 respectively; only 44/54 and 23/43 patients who were infliximab-naive with UC were evaluated at weeks 14 and 30 respectively). Missing data (excluding the 16.2% of patients who were excluded from the efficacy set) were imputed using LOCF and the manufacturer presented analyses showing similar results for clinical response and remission in CD and UC using complete case and LOCF methods.[2] The method of imputing data using LOCF, however, may overestimate treatment benefit if patients withdrew from the study because they experienced worsening of outcomes. The LOCF imputation will assume that patients who withdrew remained constant in outcome measures from the point of withdrawal and worsening in outcomes, if present, would not be captured.

While the efficacy outcomes assessed by the study were appropriate based on typical outcomes evaluated in trials of CD and UC (i.e., clinical response defined by CDAI, number of draining fistulas, Mayo score, clinical remission, endoscopic mucosal healing for UC, disease control for patients who switched from reference product, and need for rescue medication) and the thresholds used to define clinical response and remission were appropriate,[14] data are absent for other important outcomes of IBD. These other outcomes include extra-intestinal manifestations, disease biomarkers (e.g., C-reactive protein, fecal calprotectin), quality of life, and immunogenicity. Certain non-Celltrion sponsored studies provided data on disease biomarkers, but are similarly limited by observational, single arm designs. The follow-up period of 30 weeks is also too short to adequately evaluate some outcomes, such as the need for surgery and mortality. CT-P13 PMS presents preliminary, interim results and, therefore, longer-term follow-up is needed to assess if efficacy and safety outcomes remain stable. Quality of life, concern about disease flare-ups, anxiety and stress, and caregiver burden have been identified by patients as important concerns and the impact of CT-P13 on these aspects of disease are currently unknown (Appendix 3).

5.2 External Validity

The primary limitation with respect to the external validity of CT-P13 PMS is the difficulty in directly applying the results observed in patients with IBD from Korea to the Canadian population, due to differences in diet and microbiota between the countries.

The sample population of CT-P13 PMS were from study centres in South Korea. Of the treatment-naive patients, the mean age (standard deviation [SD]) was 38.9 (14.7) years (CD: 31.8 years, FCD: 27.9 years, UC: 45.2 years). Of treatment-switch patients, the mean age (SD) was 34.3 (12.4) years (CD: 31.1 years, FCD: 33.0 years, UC: 42.9 years). Most patients had moderately to severely active disease, although there were also patients with CDAI scores < 220 or partial Mayo score < 6, which indicate lower disease severity.[3] Females appeared to be underrepresented in the study (29.2% among treatment-naive and 40% among treatment-switch patients). Estimates of prevalence of IBD by sex vary among studies and by region. In European and North American populations, female-male distribution has been found to range from equal to 2.5:1.[15] There are special disease and management considerations of IBD relevant particularly to females, such as a higher incidence of extra-intestinal manifestations observed in women, which were not addressed by this study.[16]

The administered dose of CT-P13 was in accordance with the dosing recommendations of infliximab for CD and UC. CT-P13 was given intravenously starting with three doses of induction of 5 mg/kg at weeks 0, 2, and 6, and then 5 mg/kg every 8 weeks thereafter. For patients with incomplete response, the dose was increased up to 10 mg/kg. The majority (89.0%) completed the 3 doses of induction therapy. However, only 66 (38.2%) completed 6 doses of treatment by week 30. More patients in the treatment-naive group (59/113, 52.2%) received 6 doses compared with the treatment-switch group (7/60, 11.7%). The manufacturer explained that the large discrepancy in reaching 6 doses among treatment-naive and treatment-switch groups was due to differences in intervals between doses rather than any safety concerns. Treatment-naive patients were given three doses of induction within 6 weeks; whereas, switch patients received each dose at approximately 8-week intervals and, therefore, the switch group generally took beyond 30 weeks (mean: 34.5 ± 8.1 weeks) to reach dose 6.{20} The 5 mg/kg dose was received by the majority of patients (59%) and 41% received doses of 5 mg/kg to 10 mg/kg.

The study population included those who were treatment-naive (113/173, 65.3%) and treatment-switch from the reference product (60/173, 34.7%). Patients were allowed to receive premedications of analgesics (acetaminophen), antihistamines (chlorpheniramine, piprinhydrinate), or corticosteroids (hydrocortisone, dexamethasone, methylprednisolone) before or during CT-P13 infusion. At least 1 premedication was administered to 49/173 (28.3%) patients. The following concomitant medications were permitted: acetaminophen, 5-ASA with no increase in dose allowed, corticosteroids, other topical or systemic treatments for UC, and antibiotics for IBD. Rescue medications were defined as initiation of concomitant medication after the first infusion date to treat new or unresolved symptoms of CD or UC and were administered if needed. Drugs administered were antidiarrheals, intestinal anti-inflammatory/anti-infectives (e.g., sulfasalazine), systemic corticosteroids, and immunosuppressants (azathioprine). Rescue medication was administered to 48/173 (27.7%) of patients. The inclusion of treatment-naive and treatment-switch patients and the administration of premedications and/or rescue medications along with CT-P13 are reflective of clinical practice.

6. EXTRAPOLATION OF INDICATIONS

6.1 Manufacturer's Rationale for Extrapolation

The data to support the IBD indication is based on the totality of evidence collected from the quality, non-clinical, and clinical comparability exercise. A position paper prepared by CELLTRION to support extrapolation in IBD is summarized in the following sections. Refer to CT-P13 Extrapolation Position Paper which was submitted to Health Canada [30] for complete details.

a) Pathophysiology – Crohn's Disease / Ulcerative Colitis

TNFα is a pleiotropic cytokine with numerous biological functions [31] [30] and has been shown to be critical in the pathogenesis of IBD [30, page 26]. Both CD and UC are chronic inflammatory disorders that are characterized by a dysregulated mucosal immune response. In CD, inflammation is typically seen throughout the intestinal wall; whereas in UC, inflammation is typically restricted to superficial tissues e.g. the lamina propria. In IBD patients, immune cells present at the inflammation site will lead to an overproduction of TNFα [32, 33]. Mucosal inflammation in the small and large intestine due to IBD is accompanied by barrier dysfunction which leads to two main consequences. First, small solutes and water can flow into the lumen and cause leak flux diarrhea. Secondly, larger molecules and even microflora, which under normal conditions either do not or cross the epithelial barrier to only a small degree, allowing for immune tolerance induction.

TNFα signaling is also implicated in mucosal damage, as well as in the development of ulcers and fistulas via the stimulation of myofibroblasts [34]. Myofibroblasts are known to cause damage to structures of the GI tract by secreting matrix metalloproteinases (MMPs). The expression of MMPs is increased in the inflamed gut and high levels of MMPs have been associated with mucosal degradation, ulceration and fistulas [34]. As increased levels of TNFα are also present in the inflamed gut, and myofibroblasts are known to be sensitive to pro-inflammatory cytokines, TNFα has been proposed to be the initiating factor that drives the increase in MMPs. This sequence of events has recently been confirmed by [35] who have shown that TNFα is able to increase the expression of MMP-3 in human colonic myofibroblasts. The role of TNFα is also related to the induction of locally and systemically produced pro-inflammatory cytokines, increasing epithelial apoptosis and altering T-cell regulation via reverse signaling pathways [36],[37]. Damage to epithelial cells by direct effect of cytokines such as TNFα via necrosis or apoptosis can contribute to the loss of epithelial barrier. Indeed, there are significant changes in epithelial tight junction structure and function, not only in CD but also in UC. In addition, the rate of apoptosis was also found to be upregulated in UC, thereby contributing to the barrier defect. Interestingly, in non-IBD forms of colitis, such as collagenous colitis, the rate of mucosal apoptosis is not altered [38]. Additionally, inhibitory impact of TNFα and other cytokines on apoptosis of T lymphocytes residing in lamina propria can contribute to immune dysregulation and perpetual mucosal inflammation [38-40].

Also, research into granulomas has provided further evidence for the role of TNFα in promoting inflammation in CD. Granulomas consist of aggregates of macrophages, and as such represent a specialized type of inflammation. They appear to form around foreign bodies that the immune system is unable to eliminate. Granulomas are commonly found in biopsy samples from patients with CD and the formation of these cellular structures has been shown to be regulated by complex interactions between T lymphocytes and macrophages and to be dependent upon TNFα signaling [41] [30, page 27] [42].
In conclusion, TNFα is implicated in the chronic inflammation in CD and UC and is also associated with mucosal degradation, ulceration and fistulas in CD [30, page 27-29] [42, page 165]. The prolonged expression of TNFα observed in IBD and its pivotal role in the pro-inflammatory cytokine cascade

indicate that TNFα is a major driving factor of chronic inflammation in CD and UC [30, page 27] [42], page 164.

b) Mechanism of action of infliximab

Infliximab is a chimeric IgG1 mAb composed of a variable murine Fab region linked to a human IgG1κ constant region. Infliximab can bind to both the monomer and trimer forms of sTNFα [43]. The high affinity that infliximab displays towards sTNFα supports its use in inflammatory diseases such as RA, PsA, AS and PsO, UC and CD in which sTNFα signaling through binding to TNFR1 and TNFR plays a dominant role in the pathogenesis of the condition [44] [42, page 167].

Infliximab exerts its effect in the amelioration of inflammatory diseases such as CD and UC as well as RA, AS, PsA, PsO through a number of mechanisms of action. These have been evaluated in the original NDS in comparison with the reference product. They were also evaluated in the supplemental New Drug Submission (sNDS) within the 3 way similarity studies as described in Section 4.1.

1. **Binding and Neutralization of Soluble TNFα** preventing its binding to TNFRs and resulting in blocking sTNFα induced inflammatory activities including:
   - Induction of pro-inflammatory cytokines such as interleukins (IL-1 and IL-6)[45]
   - Enhancement of leukocyte migration by increasing endothelial layer permeability and expression of adhesion molecules by endothelial cells and leukocytes [46, 47]
   - Activation of neutrophil and eosinophil functional activity [47-50]
   - Induction of acute phase reactants such as C-reactive protein and other liver proteins [44], as well as tissue degrading enzymes produced by synoviocytes and/or chondrocytes [51]
   - Induction of apoptosis of tissue cells such as intestinal epithelial cells [52] through the activity of sTNFα on the TNFR1 receptor [30, page 34].
2. **Binding to Transmembrane TNFα by Infliximab:** Infliximab is able to bind to tmTNFα located on the surface of various cell types. This results in a number of effects that include:
   - Blocking the interaction of tmTNFα with TNFRs
   - Stimulation of reverse signaling pathways resulting in suppression of secretion of pro-inflammatory cytokines such as IL-1, IL-10 and IL-12 from monocytes [53, 54]
   - Induction of regulatory macrophages [55, 56]
   - Stimulation of apoptosis in monocytes [57] and T cells [58]
3. **Induction of Regulatory Macrophages and Wound Healing:** Macrophages are present in all phases of adult wound healing, and contribute to inflammation, granulation tissue formation, and matrix deposition. Both pro-inflammatory "M1" macrophages and anti-inflammatory or regulatory "M2" macrophages exist. Pro-inflammatory "M1" macrophages are produced by exposure to IFN-γ and TNFα [59] and so their production is inhibited by anti-TNF agents such as infliximab. In IBD patients, it has been shown that lamina propria macrophages are predominantly of the inflammatory or M1 phenotype [60, 61]. The anti-inflammatory M2 phenotype includes M2a, the regulatory macrophages which are activated by IL-4 and IL-13; the other M2 phenotypes are M2b and M2c [62]. Hence the ratio of M1 and M2 phenotypes are thought to be of importance in the etiology of IBD. “Regulatory” macrophages have also been termed "wound healing" macrophages [63], “Alternatively Activated Macrophages” [62] and “Mϕ2” macrophages [56]. Regulatory macrophages have been shown to inhibit T cell proliferation via cell contact and/or the release of soluble mediators [56].
4. **Complement-Dependent Cytotoxicity (CDC):** Following binding to tmTNFα on the cell surface, infliximab may induce cytotoxicity of the tmTNFα expressing cell via complement activation [58, 64]. Infliximab is of the IgG1 class and therefore can bind complement C1q. Activation of the

complement cascade can protect against infection but in inflammatory diseases could contribute to the pathology. Complement components can induce CDC of target cells resulting in cell lysis.

5. **Antibody-dependent cellular cytotoxicity (ADCC):** ADCC is the immune defense mechanisms whereby immune effector cells (e.g. macrophages or NK) bind to the Fc region on antibody-antigen complexes on the surface of target cells and thereby actively promote target cell lysis. Antibody-dependent cell-mediated cytotoxicity is mediated primarily through a set of closely related Fc receptors which have both activating and inhibitory activities, with FcγIIIa being particularly important in this respect.

   In conclusion, all the known putative mechanism of actions attributed to infliximab has been studied, and similarity to the reference product was demonstrated. Minor differences were observed in certain assays for ADCC activity that were not deemed to be clinically relevant. Please see below a summary discussion of the ADCC evaluation.

c) Justification of Extrapolation - Quality attributes and Biologic activity

Celltrion has presented the results of the 2-way similarity studies comparing CT-P13 with EU-approved REMICADE® in the original CDR submission. In support of the IBD indication; CELLTRION has performed additional large number and wide range of orthogonal, highly sensitive methods to provide a meaningful finger-print-like algorithm to assess similarity between CT-P13, EU and US approved REMICADE®. The results are highlighted in Section 4.1 above and further details are provided in Appendix 1. The comprehensive analyses have shown that CT-P13 is similar to REMICADE® in primary structure, higher order structure, aggregate and monomeric purity, and post-translational modifications notwithstanding minor differences that have been demonstrated to have no clinically meaningful impact on safety, purity or potency. The extensive ranges of *in vitro* and *ex vivo* biological assays have demonstrated similar biological activities for CT-P13 and REMICADE® in assays mimicking the mechanisms of action of infliximab in CD and UC [30, page 71].

Biologic Activity

Many *in vitro* studies reported in the literature, have found that infliximab can induce ADCC but all these studies employ engineered TNFα-overexpressing cell lines as target cells [53, 58, 65]. Notably infliximab is not observed to induce ADCC in a system comprised of naturally derived cells. Specifically, when lipopolysaccharide (LPS) stimulated human monocytes are used as target cells and PBMC as a source of effector cells, no observable ADCC is seen in response to infliximab [66]. These findings have been replicated [redacted] with purified NK cells as source of effector cells. Since LPS stimulated human monocytes are considered representative of the target cells encountered in vivo in the intestines where monocytes/macrophages are expected to be stimulated by the LPS present on the surface of commensal bacteria, these results suggest that ADCC is not likely to play a significant role in mediating the therapeutic effect of anti-TNF therapies in CD and UC. Interestingly, applying the exact same experimental system but replacing activated monocytes as the target with genetically engineered Jurkat cells which overexpress TNFα on their surface cell by approximately 25 fold does induce measurable ADCC activity using infliximab.

Further evidence that ADCC may not play a critical role in efficacy of infliximab in CD is provided by analysis of therapeutic effect of infliximab in patients of different FcγRIIIa genotype following treatment, as the binding affinity of FcγRIIIa V/V isotype for Fc region of monoclonal antibodies is higher than that of the low affinity F/F isotype. For CD, published data from several large studies [67-70] show no association between FcγRIIIa genotype and clinical response to infliximab and other TNFα-antagonists. Although differences were noted in biological response (C-reactive protein levels) in the early phases of

treatment in several CD studies, this effect did not persist to later phases of treatment, and no differences were detected in clinical outcome [68, 71].

d) Justification of Extrapolation — Pharmacokinetics

Similarity has been demonstrated between CT-P13 and REMICADE® with respect to PK parameters in AS patients and RA patients. Also, it seems scientifically justified to extrapolate PK profiles for CT-P13 across the different target populations given that the CT-P13 clinical studies show similar PK properties across AS patients and RA patients as well as between single and repeat dosing; the appropriateness of the extrapolation is further supported by published data for REMICADE® showing no major differences in half-life, clearance, volume of distribution and other PK parameters between patient subgroups and across all licensed populations [30, pages 72-80]. Furthermore, the real-world experience with CT-P13 from the sponsored Korean PMS study and non-sponsored Hungarian Nationwide IBD Study [21], [redacted].

e) Justification of Extrapolation — Efficacy and Safety

The Korean PMS study has demonstrated that CT-P13 is safe and effective in patients with CD, UC and FCD. In line with published data on REMICADE®, CT-P13 has demonstrated efficacy in terms of clinical and endoscopic response and remission, fistula-closing and mucosal healing effects.
There were no new safety signals reported in this study (please refer to Section 4.2 above for further details).

f) Justification of Extrapolation — Immunogenicity

The immunogenicity with CT-P13 and REMICADE® across CT-P13 clinical studies was similar in both RA and AS patients. Incidence rates of ADAs and neutralizing antibody levels and titer values were similar in controlled studies up to 1 year. The rates of IRRs between CT-P13 and REMICADE® were also similar. The efficacy was sustained and the pattern of efficacy and safety amongst ADA-positive and ADA-negative patients were similar between CT-P13 and REMICADE®. ADA data in IBD patients are not available, however low rates of IRRs were observed in post-marketing IBD studies with CT-P13. Furthermore *in vitro* cross-reactivity data with CT-P13 and REMICADE® against sera from ADA-positive IBD patients are available (please refer to Section 4.3 above for further details). Overall, similar and consistent immunogenicity profile with CT-P13 has been demonstrated against REMICADE® in two distinct patient populations.

g) Clinical Development to Support Dose Adjustment Recommendations

In the REMICADE® product monograph, there is the option for adult patients with CD who respond to infliximab and then lose their response to use an escalated dose of 10 mg/kg. Clinical data in IBD patients treated with CT-P13 in doses up to 10 mg/kg within the Korean PMS study have been collected. [redacted]. Overall, the efficacy according to response and safety of CT-P13 administered at higher doses to IBD patients appeared to be satisfactory, [redacted] [30, page 104].

Conclusion

In summary, CELLTRION has demonstrated clear therapeutic comparability between CT-P13 and REMICADE® in RA with supportive clinical data in AS patients. In addition, based on an extensive analysis of the totality-of-the-evidence considering mechanisms of action, structural analysis, functional assays and the similarity of pharmacokinetics, efficacy, safety and immunogenicity, combined with data from post-marketing studies CELLTRION considers that there is sufficient scientific evidence to support extrapolation of the CT-P13 to CD and UC indications for which REMICADE® is registered in Canada. A similar safety profile was demonstrated in a total of approximately 1,000 patients exposed to trial medication of which nearly 500 received CT-P13 for up to two years or for a year following transition from REMICADE®. Additionally safety data are available from 518 CD and UC patients who have received CT-P13. These data show in general a highly similar safety profile to REMICADE® across all of these populations. Immunogenicity has been shown to be highly similar in two different therapeutic settings namely RA and AS covering the effect of two different doses (3 and 5 mg/kg) and the impact of the presence or absence of MTX. Cross-reactivity studies and some limited experience with immunogenicity evaluation in CT-P13 of REMICADE®.

6.2 Health Canada's Conclusion on Extrapolation

At the time of the CDR submission, the IBD sNDS was under review by the Biologic Genetics Therapies Directorate. In June 2016, Health Canada authorized the use of CT-P13 for the IBD indications based on extrapolation from previously submitted clinical studies in patients with RA and AS, comparable pharmacokinetics, and newly submitted physiochemical and biological data.[1]

When the NDS was filed to Health Canada in 2012, market authorization was requested for all of the indications currently authorized for REMICADE® including CD and UC. The following section is taken from the Health Canada Summary Basis of Decision for INFLECTRA® [72].

"Comparability between INFLECTRA® and the reference product was established based on comparative chemistry and manufacturing studies, and comparative non-clinical studies. Comparative pharmacokinetic studies and clinical studies in patients with rheumatoid arthritis or ankylosing spondylitis patients did not identify clinically meaningful differences. For the remaining indications and uses, extrapolation was required. The indications for psoriatic arthritis and plaque psoriasis were granted on the basis of similarity and the absence of meaningful differences, between INFLECTRA® and the reference product, in product quality, mechanism of action, disease pathophysiology, safety profile, and dosage regimen and on clinical experience with the reference product. However, extrapolation to indications and uses pertaining to CD and UC could not be recommended due to differences between INFLECTRA® and the reference product that could have an impact on the clinical safety and efficacy of these products in these indications. This arose from the observed differences in the level of afucosylation, FcγRIIIa receptor binding, and some in vitro Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC) assays. It was concluded that differences in the ability of the two products to induce ADCC could not be ruled out. Therefore, since differences in ADCC have been observed between the two products and because ADCC may be an active mechanism of action for infliximab in the setting of IBD, extrapolation from the settings of rheumatoid arthritis and ankylosing spondylitis to IBD could not be recommended due to the absence of clinical studies in IBD."

Please see above, Section 6.1, for a summary of data that has since been submitted as part of a sNDS for the IBD indications to address the potential issues raised by Health Canada.

6.3 International Regulatory Conclusions on Extrapolation

European Medicine Agency (EMA)

The EMA approved CT-P13 (INFLECTRA®) for the IBD indications via extrapolation in 2013.

As per the EMA Committee for Medicinal Products in Human Use Assessment Report for INFLECTRA® [73, page 96]:

"In conclusion, by using a range of experimental models that are considered representative of the pathophysiological conditions and putative mechanisms of action of infliximab, the Applicant has provided convincing evidence that the difference detected in the amount of afucosylated species has no clinically relevant impact on the efficacy and safety of CT-P13, in particular in IBD. Additional *in vitro* data from human intestinal cells are further supporting extrapolation of the clinical data to IBD."

Food and Drug Administration (FDA)

CT-P13 has been approved by the FDA for all indications, including CD and UC via extrapolation [74]. This follows the recommendation from the US Arthritis Advisory Committee which recommended the approval of CD and UC via extrapolation of data. As per FDA Briefing Document, [75, pages 70-72]:

"Extrapolation of Data to Support Biosimilarity in Inflammatory Bowel Disease (IBD) Indications: Celltrion provided experimental data supporting a conclusion that CT-P13 and US-licensed REMICADE® are highly similar based on extensive structural and functional analytical characterization. Further, Celltrion addressed each of the known and potential mechanisms of action of US-licensed REMICADE®. As noted, there were small differences between CT-P13, US-licensed REMICADE®, and EU-approved REMICADE® in glycosylation (a-fucosylation), FcγRIII binding, and some NK-based ADCC assays. In considering whether the apparent fractional FcγRIII binding/ADCC differences may translate into a clinically meaningful difference in IBD, the Agency has considered the following:

- The biological functions that the subtle FcγRIII binding differences might impact, namely ADCC, are within the quality range of Celltrion's data on the reference product.
- The mechanism of action of TNF inhibitors in treating IBD is complex and, ADCC is only one of the several plausible mechanisms of action. It is noteworthy that products without any ADCC capability have been approved for the treatment of patients with CD (i.e. certolizumab), while the possible ADCC difference between CT-P13 and US-licensed REMICADE® is small. Celltrion has also provided data to demonstrate analytical similarity in all the other potential mechanisms of action of infliximab in IBD.
- The historical IBD clinical trial design, including those for REMICADE®, often utilized doses and timing of primary endpoint assessments that are in the therapeutic plateau, and thus clinical outcome measures (e.g., clinical effect of small differences in ADCC and FcγRIII binding.

Therefore, based on the above considerations, it is reasonable to extrapolate conclusions regarding similar efficacy and safety of CT-P13 and US-licensed REMICADE® to IBD. In aggregate, the evidence indicates that the extrapolation of biosimilarity to the indications for which Celltrion is seeking licensure (PsA, PsO, adult and pediatric CD, and adult and pediatric UC), may be scientifically justified. "

Australian Therapeutic Goods Administration (TGA)

The TGA, after evaluation from the Advisory Committee on Prescription Medicines (ACPM), approved and registered INFLECTRA® for both the CD and UC indications via extrapolation in August 2015. As per a Public Summary Document:

"The ACPM has stated there were sufficient data to declare INFLECTRA® a biosimilar for REMICADE® and to extrapolate the conclusion of equivalent efficacy from the rheumatoid arthritis and ankylosing spondylitis indications for which evidence was provided to IBD conditions" [76, page 4]

6.4 CDR Comments on Extrapolation

Health Canada considers several factors when deciding on the appropriateness of extrapolating authorization from one indication to another. These factors include:[17]

- similarity between products (minor, unimportant differences may have clinical impact)
- similarity in mechanism of action for each condition
- mechanisms of the diseases to be treated
- similarities in clinical experience
- type and design of the clinical trials, populations, and end points measured
- route of administration, dosage, and regimen.

Health Canada reviews quality information of the biosimilar compared with the reference product, assesses that the most sensitive population and best end points were included in clinical trials, and evaluates whether the biosimilar and reference product have similar safety and immunogenicity (> 100 patients and sufficiently long duration).[17]

In CADTH's previous review of Inflectra,[18] Health Canada's decisions about extrapolating data from the RA and AS indications to PsO and PsA were provided. The decision to extrapolate to PsO and PsA were supported by common disease pathologies, common mechanism of action of anti-TNF alpha drugs in these diseases, and similarities in product quality, safety, and PK. At that time, Health Canada did not support extrapolating data from RA and AS to IBD due to differences in disease mechanisms (role of tmTNF alpha and ADCC in IBD) and safety profiles of infliximab in IBD versus rheumatic diseases (higher risk of hepatosplenic T-cell lymphoma in IBD).[18] These factors are explained in more detail below, under *"Points about extrapolation identified by Health Canada."* In June 2016, Health Canada authorized the use of CT-P13 for the IBD indications based on extrapolation from previously submitted clinical studies in patients with RA and AS, comparable pharmacokinetics, and newly submitted physiochemical and biological data.[1]

Health Canada issued an NOC for Inflectra for the indications of CD, FCD, and UC on June 10, 2016. The approved indications are as follows:[19]

- Reduction of signs and symptoms, induction and maintenance of clinical remission and mucosal healing, and reduction of corticosteroid use in adult patients with moderately to severely active CD who have had an inadequate response to a corticosteroid and/or aminosalicylate. Inflectra can be used alone or in combination with conventional therapy.
- Treatment of FCD, in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment.
- Reduction of signs and symptoms, induction and maintenance of clinical remission and mucosal healing, and reduction or elimination of corticosteroid use in adult patients with moderately to severely active UC who have had an inadequate response to conventional therapy (i.e., an aminosalicylate and/or a corticosteroid and/or an immunosuppressant).

The EMA, FDA and the Australian Therapeutic Goods Administration approved CT-P13 for use in adult patients with CD and UC based on the extrapolation of efficacy and safety data for RA and AS.[20-22] These jurisdictions have also extended use to pediatric patients with CD or UC; aside from the FDA which has not approved CT-P13 for pediatric UC.

Clinical Trial Evidence for RA and AS:
Rigorous clinical trials, comparing CT-P13 with Remicade, have been conducted with PLANET-RA for RA and PLANET-AS for AS. This evidence was evaluated in detail in the previous CADTH submission for Inflectra.[18] PLANET-RA was a phase III RCT in patients with RA (N = 606). CT-P13 or Remicade were administered at 3 mg/kg along with MTX plus folic acid. The trial demonstrated no differences in efficacy, safety, immunogenicity (development of ADA), or PK. PLANET-AS was a phase I RCT in patients with AS (N = 250). CT-P13 or Remicade were administered at 5 mg/kg. Similar PK, efficacy, safety, and immunogenicity were demonstrated.[18]

Points About Extrapolation Identified by Health Canada:
In the pathology and mechanisms of action of anti-TNF alpha drugs for RA, AS and IBD, some differences exist that presented uncertainties in extrapolating between these disease conditions. The predominant form of TNF in RA and AS is sTNF alpha; whereas, in CD and UC, tmTNF alpha plays an additional and central role by initiating reverse signalling pathways.[23] Also, unlike RA and AS, in bowel diseases ADCC is an important mechanism of action and is mediated by afucosylation and FcγIIIa receptor binding. Minor differences have been observed between CT-P13 and the reference product in FcγIIIa binding and ADCC activity using in vitro assays with NK cells from patients with CD and V/V or V/F FcγIIIa genotype (no difference observed with F/F genotype). In other assays using PBMCs from patients with CD and V/F or F/F FcγIIIa genotype, no difference in ADCC activity was observed.[24] The clinical relevance of differences in ADCC activity may be minor. Etanercept is another anti-TNF alpha drug that is clinically effective in RA but not in IBD, possibly because it is less efficient at reverse signalling and apoptosis.[23] However, the structure of etanercept differs from infliximab and this results in a distinct efficacy profile.[23] CT-P13 was shown to be comparable to the reference product with respect to reverse signalling and apoptosis.[19] Hepatosplenic-T cell lymphoma has been observed to occur at a higher incidence in adolescent and young adult males with CD or UC who are treated with infliximab in combination with azathioprine or 6-mercaptopurine.[19]

Other Considerations About Extrapolating to IBD:
The clinical management of IBD differs from RA and AS. For example, MTX is an immunosuppressant that is not administered as frequently for IBD as it is for RA or AS. The use of MTX in combination with infliximab has been shown to reduce the development of immunogenicity (i.e., the formation of ADA against infliximab).[23] The development of immunogenicity is a critical factor in the loss of response to biological drug treatment.[25] The effect of other medication regimens on immunogenicity that are administered with infliximab in IBD, such as azathioprine, corticosteroids, or 5-ASA, is unclear. In a study of 174 patients with CD, concomitant administration of MTX or azathioprine with infliximab was found to reduce the incidence of ATI formation (46% versus 73% with infliximab monotherapy); however, no differences in ATI formation were observed between infliximab plus MTX and infliximab plus azathioprine.{44} Further investigation of the effect of immunosuppressant regimens on immunogenicity is needed. Secondly, the maximum dose of infliximab for IBD is 10 mg/kg and is higher than the doses used in PLANET-RA or PLANET-AS. Although in vitro studies with the sera of patients with IBD who developed

ADA after Remicade were found to be cross-reactive with CT-P13, suggesting similar features of immunogenicity (Section 4.4), the immunogenic similarity of the higher dose of CT-P13 with regular or higher doses of Remicade is uncertain. There is also a microbiological component to IBD that is absent in RA or AS. Patients with IBD are at high risk for bacteremia/sepsis and infections such as shingles, skin infections, and pneumonia and require close monitoring, especially during treatment with infliximab.

7. COST COMPARISON

The Inflectra 100 mg/vial drug product will carry a 44% lower price ($525.0000) relative to the currently lowest-listed price of Remicade 100 mg/vial, which is at $940.0000 per the Régie de l'assurance maladie du Québec (RAMQ). Consequently, the 44% cost differential equates to $415.0000 savings per 100 mg vial. Please note that the List Price of REMICADE® in all other Provinces in Canada (excluding Quebec) is $987.0000 per 100 mg vial. Therefore the cost savings of INFLECTRA® versus REMICADE® in provinces outside Quebec (47% or $462 less expensive than REMICADE®) is actually greater than what is shown in the following tables

TABLE 5: COST COMPARISON OF INFLECTRA AND REMICADE FOR CROHN'S DISEASE (FIRST YEAR)

Drug / Comparator	Strength	Dosage Form	Price ($)	Recommended Dose[c]	Average Drug Cost ($)/Year
Inflectra	100 mg/vial	Lyophilized power	$525.0000[a]	5 mg/kg	$16,800
Remicade	100 mg/vial	Lyophilized power	$940.0000[b]	5 mg/kg	$30,080

[a] Public price.
[b] RAMQ List of Medications, updated 2016-02-08.
[c] Inflectra and Remicade product monograph.

TABLE 6: COST COMPARISON OF INFLECTRA AND REMICADE FOR CROHN'S DISEASE (SUBSEQUENT YEAR)

Drug / Comparator	Strength	Dosage Form	Price ($)	Expected Dose[c]	Average Drug Cost ($)/Year
Inflectra	100 mg/vial	Lyophilized power	$525.0000[a]	5mg/kg	$14,700
Remicade	100 mg/vial	Lyophilized power	$940.0000[b]	5mg/kg	$26,320

[a] Public price
[b] RAMQ list of Medications, updated 2016-02-08
[c] Inflectra and Remicade product monograph

TABLE 7: COST COMPARISON OF INFLECTRA AND REMICADE FOR ULCERATIVE COLITIS (FIRST YEAR)

Drug / Comparator	Strength	Dosage Form	Price ($)	Recommended Dose[c]	Average Drug Cost ($)/Year
Inflectra	100 mg/vial	Lyophilized power	$525.0000[a]	5 mg/kg	$16,800
Remicade	100 mg/vial	Lyophilized power	$940.0000[b]	5 mg/kg	$30,080

[a] Public price.
[b] RAMQ list of Medications, updated 2016-02-08.
[c] Inflectra and Remicade product monograph.

TABLE 8: COST COMPARISON OF INFLECTRA AND REMICADE FOR ULCERATIVE COLITIS (MAINTENANCE AT EVERY 7 WEEKS[A]), (SUBSEQUENT YEAR)

Drug / Comparator	Strength	Dosage Form	Price ($)	Expected Dose[c]	Average Drug Cost ($)/Year
Inflectra	100 mg/vial	Lyophilized power	$525.0000[a]	5 mg/kg	$14,700
Remicade	100 mg/vial	Lyophilized power	$940.0000[b]	5 mg/kg	$26,320

[a] Public price.
[b] RAMQ list of Medications, updated 2016-02-08.
[c] Inflectra and Remicade product monograph.

CDR Reviewer Comments Regarding Cost Information

Summary of the Manufacturer's Analysis

SEB infliximab (Inflectra) is available as a 100 mg/vial solution for intravenous infusion at a manufacturer submitted price of $525.00 per vial.[27] The manufacturer submitted a cost comparison between Inflectra and reference infliximab (Remicade) for three indications: adult patients with moderately to severely active CD, FCD, and UC.[27] The manufacturer assumed a weight-based dose of 5 mg/kg for Inflectra and Remicade for the three reviewed indications. Under the assumption of similar effect and usage of the interventions, the cost savings of Inflectra compared with Remicade were reported to be 44% of the manufacturer's base case; using the RAMQ (Quebec) list price for Remicade ($940.00 per 100 mg vial). For the other Canadian jurisdictions, the difference was reported to be up to 47% of the manufacturer's base case (Remicade price: $987.00 per 100 mg vial).[27]

CDR Assessment of the Manufacturer's Cost Comparison

- Using the Ontario Exceptional Access Program (EAP) price of Remicade as a reference, [28] the annual cost of Inflectra is 47% lower than that of Remicade (refer to Table 9).

TABLE 9: INFLIXIMAB DOSING BASED ON THE MANUFACTURERS COST COMPARISON

Treatment/ Indications	Time Period	Recommended Dose[a]	Number of Treatments/ Year[a]	Price per 100 mg Vial($)[b]	Annual Cost($)[c]
Inflectra/ CD and UC	First year	5 mg/kg	8	525.0000	16,800
	Subsequent years	5 mg/kg	6.5	525.0000	13,650
Remicade/ CD and UC	First year	5 mg/kg	8	987.5600	31,601
	Subsequent years	5 mg/kg	6.5	987.5600	25,677

CD = Crohn's disease; UC = ulcerative colitis.
[a] Inflectra and Remicade product monograph.
[b] Manufacturer submitted price for Inflectra; [27] Ontario EAP price for Remicade. [28]
[c] Assumes patient weight is between 60 kg to 80 kg.

Issues for Consideration

- Given the complexities of managing IBD, the clinical expert noted that physicians and patients may be reluctant to switch from Remicade to Inflectra when a patient is adequately managed on Remicade. As a result, Inflectra may be more likely to be used in patients who are newly starting infliximab rather than those switching from Remicade.
- The manufacturer of Remicade sponsors infusion centres for the administration of Remicade, and covers costs of patient follow-up and monitoring. These costs are expected to be similarly covered by the manufacturer of Inflectra, therefore, this is not expected to result in additional costs to the publicly funded health care payer.[10]
- The dosage of Inflectra is based on patient weight. Considering that Inflectra and Remicade have similar pharmacokinetics, pharmacodynamics, clinical efficacy and harms, and share the same dosing strategies, the relative cost difference between the drugs is therefore likely to be maintained regardless of patient characteristics or required daily dose.
- Based on the product monograph, the dose of infliximab in patients with UC and CD can be increased to up to 10 mg/kg.[19] Dose escalation would similarly impact the cost of both Inflectra and Remicade, the relative cost difference would therefore not be affected. However, this could affect

the cost differential with other treatments for these indications.

- Inflectra (SEB infliximab) was previously reviewed by CADTH for four indications: RA, AS, PsA, and PsO. It was recommended that Inflectra be listed in accordance with the Health Canada indication and in a similar manner to Remicade.[29]
- The listing criteria for Remicade differ across publicly funded drug plans in Canada; whereas, Remicade is available as a restricted benefit with specific listing criteria (Appendix 2). The expected savings from Inflectra compared with Remicade are based on the assumption that the listing criteria for Remicade would be applied to Inflectra.

Conclusion

At the submitted price, the annual cost of Inflectra is 47% less than the reference product infliximab (Remicade) when using the Ontario EAP price for Remicade ($987.56) as a reference.

8. DISCUSSION

Biological drugs are important treatment options for inducing and maintaining remission of CD and UC. In Canada, the three anti-TNF alpha drugs approved for IBD are infliximab, adalimumab, and golimumab.[23] These drugs may be used in step-up or step-down treatment approaches. In the step-up approach, 5-ASA is prescribed initially, followed by corticosteroids (e.g., topical foams, budesonide, prednisone), immunosuppressants (e.g., azathioprine, MTX), and anti-TNF alpha drugs if symptoms are not controlled. In the step-down approach, drugs at the higher end of the treatment ladder are initiated first, followed by downward titration to the drug(s) that offer the most favourable profile of symptom control and minimization of adverse effects.[30] CT-P13 is a biosimilar of the reference infliximab product, Remicade, and offers another, potentially cost-effective, treatment option for CD and UC. A biosimilar product is designed to be similar to a reference product that is already being used in clinical practice. The molecular complexity of biologics compared with other drugs requires close scrutiny of the biosimilar's PK, efficacy, safety, and immunogenicity.

The clinical evidence for the use of CT-P13 in IBD was based on observational trials. No direct comparisons with Remicade in this patient population were available. Data from *in vitro* studies suggest similar immunogenicity, sTNF alpha and tmTNF alpha binding, and ADCC activity using PMBCs among CT-P13 and Remicade, although differences in ADCC activity using NK cells were observed. Some differences between IBD and RA or AS exist, such as the greater roles of tmTNF alpha and ADCC, higher infliximab dosing requirements, and administration of different immunosuppressant treatment regimens in IBD. The results of the ongoing RCT (CT-P13 3.4) are anticipated to provide additional evidence to assess the efficacy and safety of CT-P13 compared with Remicade in IBD. In addition, the experiences of jurisdictions that are already using CT-P13 for IBD, such as the US, Korea, and various European countries, can be used as a guide for the ongoing assessment of its efficacy and safety. No new safety signals have emerged, although continued long-term monitoring is needed.

The Canadian Association of Gastroenterology has issued a position statement on SEBs for IBD.[31] They support the use of biosimilars as potentially effective and cost-saving options, but emphasize that evidence from clinical trials relevant to Canadians should be available to support their use in practice. Patient groups for IBD have also voiced their concerns about therapies being chosen based solely on considerations of cost (Appendix 3). They have indicated that disease remission can be difficult to obtain and that changes to therapy, including switching from an innovator product to an SEB, should not be made without a patient's consent. Expert knowledge, open-dialogue, and patient choice will be integral to effectively implementing CT-P13 in clinical practice. Health care providers and patients should be provided with information about Health Canada's SEB regulatory process, the clinical evidence available for CT-P13, and the rationale behind extrapolation.

Post-marketing data of CT-P13 will be critical for monitoring expected and new safety signals and to ensure that benefits outweigh risks in both treatment-naive and treatment-switch patients. Assessment of immunogenicity and incidence of serious side effects, such as hepatosplenic T-cell lymphoma, will be needed for evaluating CT-P13's risk-benefit profile. Given the interim nature of the CT-P13 PMS study, it will be important to assess if the observed results remain stable over several years.

Potential Place in Therapy[2]

The reference infliximab product, Remicade, is currently used for patients with moderate to severe CD and UC alone or in combination with immunomodulators such as azathioprine. It is effective in treating perianal disease as well as luminal inflammation. Occasionally patients are started on Remicade immediately upon diagnosis, but more often both private insurers and public drug plans indicate that patients should first have been inadequately managed with 5-ASA, steroids, and immunomodulators such as azathioprine. Remicade has a similar action and efficacy to other anti-TNF alpha drugs, and is administered under supervision at infusion centres. For some patients, contact with health providers on a regular basis is helpful, while for others, self-administration is preferred, in which case another anti-TNF alpha drugs, such as adalimumab, may be used.

CT-P13 is an SEB that does not add to available therapy options but provides a less expensive alternative to an established therapy. It is not designed to be novel but to be similar to the reference product (Remicade). A significant percentage of patients with IBD do not have insurance for the cost of medications, often because the disease affects younger individuals who may not yet have drug plan insurance.[32] Following disease onset, insurance is very difficult to obtain. Therefore, the potential cost savings of CT-P13 in this population would be advantageous.

Both private and public drug plans have guidelines in place that stipulate which patients are eligible for treatment with anti-TNF alpha drugs, and CT-P13 will fit within that framework. An important question, which will need to be addressed if the drug is introduced, is whether patients who are stable on Remicade will have the drug substituted with CT-P13 or whether it will only be used in treatment-naive patients. Endoscopic evaluation of disease activity may be required in patients who experience a disease flare after switching, and there are significant barriers to that in terms of access to endoscopy procedures. Observational cohort studies from different countries suggest that disease activity and adverse effects are similar before and after switching. However, given the limitations of observational studies, the assessment and prediction of patient response upon switching from Remicade to CT-P13 will require close monitoring.

[2] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

9. CONCLUSION

CT-P13 provides clinicians and patients with another potentially cost-effective choice of a biological drug for IBD. The focus of this CDR review of CT-P13 (Inflectra) is for the recently approved indications of CD, FCD, and UC in adult patients. The Notice of Compliance (NOC) for the CD, FCD, and UC indications was granted subsequent to an earlier NOC for CT-P13 for the indications of RA, AS, PsO, and PsA. Of note, Health Canada approved the indications of PsO and PsA based on the extrapolation of data from studies conducted with patients with RA and AS. All clinical evidence currently available for CT-P13 in patients with IBD is based on observational, open-label studies from Korea or Europe in small numbers of patients. The pivotal study, CT-P13 PMS, is an observational, open-label study conducted in South Korea in patients with IBD, with a 30-week interim analysis. Naive indirect comparisons of CT-P13 with studies of Remicade (infliximab) suggest similar efficacy and similar safety for some safety end points in patients with CD or UC. Nonetheless, in the absence of data from RCTs, the clinical similarity of CT-P13 and Remicade for IBD in the Canadian population remains uncertain. Given that the results of CT-P13 PMS are based on an interim analysis, the ongoing monitoring of CT-P13 in patients with IBD will be important for evaluating long-term efficacy and safety.

APPENDIX 1: ADDITIONAL DATA

Please include any large tables or figures in this section of the template. Please ensure the following is included:

- All items in this section must be well-labelled (e.g., Table 6: Adverse Events from Study X).

All items in this section must be clearly referenced in the main body of the template. For example, "please see Table 6 in Appendix 1 for complete details regarding the adverse events reported in the Study X."

TABLE 10: HIGH LEVEL OVERVIEW OF THE TESTS AND CONCLUSIONS FOR THE OLIGOSACCHARIDE PROFILING AND BIOLOGIC ACTIVITY COMPARISON BETWEEN CT-P13 AND REMICADE®

Type of study(s)	Brief overview of tests and conclusions	References
Binding of soluble and transmembrane TNFα		
Oligosaccharide profiling	• HPAEC-PAD Test • To characterize the glycan micro-heterogeneity associated with the single site of N-glycosylation (Asn300), glycans were enzymatically cleaved using PNGase F and resolved using chromatography. • The HPAEC-PAD data reveal that the type and proportion of the uncharged glycans is reasonably conserved between CT-P13, EU and US approved REMICADE®. • Minor differences in afucosylated glycans: mean values of Man5+G0, for EU and US approved REMICADE® by HPAEC-PAD were [redacted], respectively, compared to [redacted] FOR CT-P13.	CTD Module 3.2.R.2.7
Effect of blocking soluble TNFα *in vitro* IBD model	• Inhibition of Inflammatory Cytokines (IL-8) from Caco-2 cells test • The ability of CT-P13, EU and US approved REMICADE® to inhibit release of inflammatory cytokines (IL-8) from an intestinal epithelial cell line following stimulation with cytokines (TNF-α, IL-1, LPS and IFN-γ) was evaluated. • The data indicate that the 3 products are comparable in relative suppression of cytokine in CaCo-2 cells with mean± SD values for CT-P13, EU and US approved REMICADE®.	CTD Module 3.2.R.2.8.1.6
tmTNFα Receptor Signaling Studies	• Suppression of cytokine release by reverse signaling test • This method was developed to measure reverse signaling resulting from samples binding to tmTNFα and resulting in inhibition of LPS-induced cytokine release (TNFα) from Peripheral Blood Mononuclear cells (PBMCs). • PBMCs from healthy subjects were isolated and then incubated, with samples over a range of concentrations. • The relative inhibition of cytokine release induced by reverse signaling on binding of CT-P13 is similar to that of EU and US approved REMICADE®. The mean values for each concentration also indicate comparable activity of the 3 products in inhibition of cytokine release by reverse signaling.	CTD Module 3.2.R.2.8.1.5

Type of study(s)	Brief overview of tests and conclusions	References
	• Induction of apoptosis by reverse signaling test • Apoptotic activity, resulting from antibody-induced signaling after binding to transmembrane was conducted using the recombinant Jurkat cell line which stably expresses tmTNFα. • The apoptosis assay was performed using a commercially available kit which labels cells using Annex in-V/PI to determine the number of apoptotic cells. • The relative induction of apoptosis through reverse signaling of CT-P13, EU and US approved REMICADE® are similar.	CTD Module 3.2.R.2.8.1.4
Fc f(ab')2 related		
Evaluation of Regulatory Macrophage Function	• Effect of Infliximab on Suppression of T Cell Proliferation by Regulatory Macrophages in Mixed Lymphocyte Reaction (MLR) Assay • The MLR requires mixing of Human Leukocyte Antigen disparate PBMC from 2 individuals that are nonetheless matched for FcγRIIIa genotype. • CT-P13, EU and US approved REMICADE® induced regulatory macrophages in the MLR assay. Similarity was observed between CT-P13 and EU and US approved REMICADE® at all concentrations.	CTD Module 3.2.R.2.8.2
	• Quantitation of Infliximab-Induced Regulatory Macrophages by FACS • A dose-dependent inhibition of T cell proliferation of PBMCs from healthy donors was induced by CT-P13 EU and US approved REMICADE®. • Similar activity was detected for the 3 products.	
	• Effect of Wound Healing by Regulatory Macrophages • The effect of the induced macrophages on scratches in a colorectal cell layer (HCT 116) was determined in a wound healing assay. • Wound healing models using bidirectional (V/F+V/F) MLR with PBMC from healthy donors and demonstrated that there was comparable activity for CT-P13 and EU and US approved REMICADE® with respect to the ability of induced regulatory macrophages to promote wound healing.	
CDC Studies	• Complement-dependent cytotoxicity (CDC) Activity • C1q-binding is followed by activation of C1q enzymatic activity and subsequent activation of the downstream complement cascade. The level of cytotoxic activity was measured by viable cell counting using a kit. • The mean relative binding values for CT-P13, EU and US approved REMICADE® were similar.	CTD Module 3.2.R.2.8.3.2
	• C1q binding affinity (ELISA) • Binding affinity of CT-P13 EU and US approved REMICADE® to C1q was measured by ELISA. • The mean relative binding values CT-P13, EU and US approved REMICADE® were similar for C1q binding	CTD Module 3.2.R.2.8.3.1

Type of study(s)	Brief overview of tests and conclusions	References
	affinity.	
Fcγ receptor Binding Studies	• Comparative binding to Fcγ receptors: FcγRI binding affinity (ELISA), FcγRIIa, FcγRIIb and FcRn binding affinity • The mean relative binding affinity values FOR CT-P13, EU and US approved REMICADE® show that the 3 products have comparable in FcγRIIa, FcγRIIb and FcRn binding affinity The three products have been demonstrated to have similar binding affinity.	CTD Module 3.2.R.2.8.4
	• Comparative binding to Fcγ receptors: FcγRIIIa (V and F hemizygotes) and FcγRIIIb binding affinity (SPR) • Using the [redacted] instrument, the binding of CT-P13, EU and US approved REMICADE® was measured in real time at 3 concentrations to the immobilized FcγRIIIa (V type) ligand by measuring changes in the refractive index. • The results demonstrate that the FcγRIIIa (V type) binding affinity of EU and US approved REMICADE® batches was significantly higher than for CT-P13, confirming the data obtained in the previous study submitted in the NDS showing FcγRIIIa (V type polymorphic variant) binding affinity is dependent on the afucosylation level (CTD Module 3.2.R.5, Sequence 0000). • This difference in binding between CT-P13 and REMICADE® is much smaller than the difference in binding to FcγRIIIa of different genotypes. Studies have failed to discern a clinical difference in response (Crohn's Disease Activity Index [CDAI]) following infliximab treatment between CD patients expressing the low affinity F/F genotype compared to those expressing the high affinity V/V genotype [67]. • The mean relative binding affinity values INFLECTRA®, EU and US approved REMICADE® indicate some difference in binding affinity to FcγRIIIb although [redacted] batches of INFLECTRA® were within the mean±3SD of EU approved REMICADE® batches and [redacted] batches were within the mean±3SD of US approved REMICADE® batches. • The clinical relevance of any possible differences in FcγRIIIb binding affinity were investigated in previous studies submitted in the NDS comparing the ability of CT-P13 and EU approved REMICADE® to bind to Neutrophils, which express predominantly FcγRIIIb on the cell surface. These studies were presented in CTD Module 3.2.R.5 (Sequence 0000) and demonstrated that there is no difference in binding of CT-P13 and EU approved REMICADE® to neutrophils from healthy volunteers and CD patients. Thus, any difference observed in binding affinity to FcγRIIIb by SPR appears to have no clinical significance.	CTD Module 3.2.R.2.8.4.1 CTD Module 3.2.R.2.8.4.2

Type of study(s)	Brief overview of tests and conclusions	References
	• Comparative binding to Rcy receptors: *Ex vivo* assay (NK cells from Healthy PBMC • To assess if the differences between CT-P13, EU and US approved REMICADE® in FcγRIIIa (V-type and F-type polymorphic variants) binding as determined by SPR translate into functional differences related to binding to the FcγRIIIa present on NK cells, *ex vivo* NK cell binding studies were conducted in the 3-way abridged study. NK cells are known to express FcγRIIIa on their cell surface and serve as suitable *ex vivo* model for the assessment of FcγRIIIa binding. • The mean relative binding of CT-P13, EU and US approved REMICADE® in the presence of 1% bovine serum albumin show some difference between CT-P13 and REMICADE®. However in the more physiologically representative conditions in the presence of 50% human serum, the mean relative binding of CT-P13, EU and US approved REMICADE® have comparable binding to FcγRIIIa on NK cells, although one batch of INFLECTRA® with a value of [redacted] relative binding to NK cells *ex vivo* in 50% serum was below the mean-3SD of US approved REMICADE® of [redacted]. • The difference observed in *ex vivo* NK cell binding between CT-P13 and EU approved REMICADE® is small in comparison to the difference in binding of EU approved REMICADE® to FcγRIIIa of different genotypes.	CTD Module 3.2.R.2.8.4.8
ADCC Potency studies using different effector and target cells	• ADCC using PBMC from Healthy donors • The ADCC assay using transfected tmTNFα Jurkat cells as target cells and PBMC from healthy donor of V/F FcγRIIIa genotype as effector cells was conducted using [redacted] batches each product. • PBMC of FcγRIIIa genotypes were used in this study ADCC using PBMC from Healthy donors. • The mean relative ADCC activity of CT-P13, EU and US approved REMICADE® show similar ADCC activity between INFLECTRA® and REMICADE® using transmembrane TNFα Jurkat target cells and PBMC effector cells. All batches of INFLECTRA® were within the mean±3SD range of both EU and US approved REMICADE® batches using this assay system.	CTD Module 3.2.R.2.8.5.1
	• ADCC using NK cells from Health donors • The ADCC assay using transfected tmTNFα Jurkat cells as target cells and NK cell isolated from PBMC of V/F FcγRIIIa healthy donors as effector cells. • The mean relative ADCC activity of CT-P13, EU and US approved REMICADE® indicate some slight difference in ADCC activity between CT-P13 and REMICADE® using transmembrane TNFα Jurkat target cells and NK effector cells.	CTD Module 3.2.R.2.8.5.1 CTD Module 3.2.R.2.8.5.2
	• ADCC using Lipopolysaccharide (LPS)-stimulated monocytes as target cells	CTD Module 3.2.R.2.8.5.3

Type of study(s)	Brief overview of tests and conclusions	References
	• The ability of the LPS-stimulated monocytes isolated from healthy donor to act as targets in an ADCC assay was investigated among CT-P13, EU and US approved REMICADE®. • The data show no ADCC activity was detectable for CT-P13, EU and US approved REMICADE®. • These findings suggest that LPS-stimulated monocytes, supposed to be representative of inflammatory foci *in vivo*, do not express sufficient amounts of tmTNFα to induce an effective ADCC in response to the presence of CT-P13, EU and US approved REMICADE®.	
	• *Ex vivo* tmTNFα Expression Level in IBD Patients • Biopsy material was obtained from [redacted] patients with mild to severe UC or CD and the level of tmTNF expression on Lamina Propria Mononuclear Cells from these IBD patients has been investigated. • The data clearly show that monocytes and macrophages in the lamina propria of IBD patients express low levels of tmTNF. The expression of tmTNF on monocytes/macrophages was approximately [redacted] lower than on monocytes/macrophages from LPS stimulated PBMCs from healthy donors and tmTNF was expressed at only 2% (50 fold lower) of the level obtained with tmTNFα Jurkat cells. • These data confirm that low levels of tmTNFα are expressed on monocytes/macrophages in lamina propria of IBD patients and together with data from ADCC studies suggest that ADCC is highly unlikely to contribute to therapeutic effect in IBD.	CTD Module 3.2.R.2.8.5.4

REMICADE® PHARMACOKINETIC LINEARITY

Concentration Versus Time Curve of Infliximab treatment with and without Methotrexate (MTX):
Data for the serum infliximab log concentration versus time curve for RA patients treated with 3 and 10 mg/kg infliximab supports a dose-proportional PK prolife, regardless of the presence or absence of MTX [77, 78].

In the CO168T14 trial, assessing 101 RA patients treated with 1, 3 or 10mg/kg or placebo either alone or in combination with 7.5 mg/kg MTX, there was no apparent dose- or concentration-efficacy response for 3 or 10 mg/kg dosing at every 4 weeks or every 8 weeks [79, 80]. The plasma concentration of infliximab was slightly increased with the use of MTX, with the most profound effect seen with low dose 1mg/kg [77-80]. A dramatic decrease in serum infliximab concentration was observed for the 1mg/kg dose given without MTX, and thought to be a result of increased infliximab clearance due to Human Anti-chimeric Antibody formation [77-80]. Regardless of MTX administration, the infliximab 3 and 10 mg/kg doses were associated with similar efficacy. The duration of clinical response in the 1 mg/kg dose without MTX was markedly shorter than 1 mg/kg with MTX [77].

The pivotal Phase III ATTRACT trial, assessing 428 patients treated with 3 or 10 mg/kg (with MTX) or placebo (with MTX) at 4- or 8-week intervals, showed maximum infliximab serum concentrations to be directly proportional to intravenous dose over a 3 mg/kg to 10 mg/kg range [81]. The infliximab medium

serum concentration was 3.2-3.3-fold higher for 10 mg/kg dose compared to 3 mg/kg dose, administered every 8 weeks through 14 weeks of treatment [80].

Infliximab serum Accumulation:
Infliximab could be detected in the serum of most patients for at least 8 weeks after a single dose of 5 mg/kg for Crohn's disease and the RA maintenance dose of 3 mg/kg every 8 weeks [82]. Repeated administration of infliximab (5 mg/kg at 0, 2 and 6 weeks in fistulising Crohn´s disease, 3 or 10 mg/kg every 4 or 8 weeks in RA) resulted in a slight accumulation of infliximab in serum after the second dose [83]. No systemic accumulation of infliximab was observed in continued repeated treatment with 3mg/kg or 10mg/kg at 4- or 8- week intervals in RA patients or in severe Crohn's disease patients retreated with 4 infusions of 10mg/kg at 8 week intervals [11, 82] [12].

Infliximab Volume of Distribution and Clearance:
The volume of distribution of infliximab at steady state (4-5.6 L in a 70 kg individual) is not dependent on the administered dose and indicates that infliximab is distributed primarily within the vascular compartment [11, 84] [12]. There is a very low systemic clearance of infliximab of about 11-15 mL/hour and the elimination half-life of infliximab can range 7.7-14.7 days [11, 77, 82]. There are no specific studies assessing the metabolism or excretion of infliximab in humans [77]. It is believed that infliximab is eliminated in a similar manner to other proteins [11]. There are no major differences in clearance or volume of distribution of infliximab in patients sub grouped by age or weight [11, 12, 78].
Anti-drug antibody development has been associated with increased clearance of infliximab in UC patients [12], while higher serum albumin concentrations were associated with decreased clearance of infliximab in patients with UC [12]. Human Anti-chimeric Antibody formation is associated with increased clearance of infliximab and a decreased exposure, based on area under the curve, when MTX is not co-administered [78, 79, 81]. This increase in clearance is dose-dependent and the highest level of clearance is observed with the 1 mg/kg dose [78, 79, 81]

APPENDIX 2: DRUG PLAN LISTING STATUS FOR REFERENCE PRODUCT

For each indication that is approved by Health Canada for the SEB (or likely to be approved, in the case of a submission filed on a pre-NOC basis), please provide the publicly available listing status and criteria for the reference product.

Step 1: Use the following abbreviations to complete the table. Use a separate row for each indication and add more rows if necessary.

Abbreviation	Description
EX	Exception item for which coverage is determined on a case-by-case basis
FB	Full benefit
NB	Not a benefit
RES	Restricted benefit with specified criteria (e.g., special authorization, exception drug status, limited use benefit)
UR	Under review

Listing Status for REMICADE®

Indication(s)	CDR-Participating Drug Plans													
	BC	AB	SK	MB	ON	NB	NS	PE	NL	YK	NT	NIHB	DND	VAC
Crohn's Disease	**RES**	**RES**	**RES**	**RES**	**RES**	**RES**	**RES**	**RES**	**RES**	**RES**	**RES**	**RES**	**RES**	**RES**
Ulcerative Colitis	**NB**	**RES**	**RES**	**RES**	**RES**	**NB**	**NB**	**NB**	**NB**	**RES**	**NB**	**NB**	**NB**	**NB**

AB = Alberta, BC = British Columbia, DND = Department of National Defence; MN = Manitoba; NIHB = Non-Insured Health Benefits Program; NL = Newfoundland and Labrador; NS = Nova Scotia; NT = Northwest Territories; ON = Ontario; PE = Prince Edward Island; SK = Saskatchewan; VAC =Veterans Affairs Canada; YK = Yukon.

Step 2: For all restricted benefit entries (RES), please state the criteria used by each drug plan. Use a separate table for each indication and add or delete rows as necessary.

Restricted Benefit Criteria for REMICADE® for the treatment of Crohn's Disease

Drug Plan	Criteria for Restricted Benefit
BC	Treatment of moderate to severe active Crohn's disease or fistulising Crohn's disease according to established criteria when prescribed by a gastroenterologist Active Crohn's Disease CURRENT HARVEY BRADSHAW INDEX greater than 8 Resistant, dependent, contraindicated or intolerant to corticosteroids -corticosteroid resistant: lack of a symptomatic response despite a course of oral prednisone 40-60mg/day (or equivalent) for a minimum of 14 days. -corticosteroid dependent: unable to withdraw oral corticosteroid within 3 months of initiation without a recurrence of symptoms; a symptomatic relapse within 3 months of stopping; or the need for two or more courses of corticosteroids within one year. -corticosteroid use is contraindicated (specify): -intolerant/side effect(s) (specify): FOR PATIENTS WITH FISTULIZING CROHN'S Failure with, intolerance to or contraindication to: Ciprofloxacin at maximally tolerated doses (min 3 week trial) Metronidazole at maximally tolerated doses (min 3 week trial) For Renewal CURRENT HARVEY BRADSHAW INDEX SCORE WHILE ON TREATMENT REQUIRES HBI SCORE <5 OR A DECREASE IN SCORE >4.
AB	Moderately to Severely Active Crohn's Disease and Fistulising Crohn's Disease: "Special authorization coverage may be approved for coverage of infliximab for the reduction in signs and symptoms and induction and maintenance of clinical remission of Moderately to Severely Active Crohn's Disease and/or treatment of

Drug Plan	Criteria for Restricted Benefit
	Fistulising Crohn's Disease in patients who meet the following criteria: - Infliximab must be prescribed by a Specialist in Gastroenterology or a physician appropriately trained by the University of Alberta or the University of Calgary and recognized as a prescriber by Alberta Blue Cross for infliximab for coverage for the treatment of Moderately to Severely Active Crohn's Disease and/or Fistulising Crohn's Disease patients (`Specialist'). - Patients must be 18 years of age or older to be considered for coverage of infliximab. - Patients will be limited to receiving one dose of infliximab per prescription at their pharmacy. - Patients may be allowed to switch from one biologic agent to another following an adequate trial of the first biologic agent if unresponsive to therapy (both primary loss of response and secondary loss of response) or due to serious adverse effects or contraindications. An adequate trial is defined as at a minimum the completion of induction dosing (e.g. initial coverage period). - Patients will not be permitted to switch back to a previously trialed biologic agent if they were deemed unresponsive to therapy. - Patients are limited to receiving one biologic agent at a time regardless of the condition for which it is being prescribed. Prior to initiation of infliximab therapy for New Patients: 'New Patients' are patients who have never been treated with infliximab by any health care provider. Moderately to Severely Active Crohn's Disease: Prior to initiation of infliximab therapy, New Patients must have a current Modified (without the physical exam) Harvey Bradshaw Index score of greater than or equal to 7 (New Patient's Baseline Score), AND be Refractory. Refractory is defined as one or more of the following: 1) Serious adverse effects or reactions to the treatments specified below; OR 2) Contraindications (as defined in product monographs) to the treatments specified below; OR 3) Previous documented lack of effect at doses and for duration of all treatments specified below: a) mesalamine: minimum of 3 grams/day for a minimum of 6 weeks; AND refractory to, or dependent on, glucocorticoids: following at least one tapering dosing schedule of 40 mg/day, tapering by 5 mg each week to 20 mg, then tapering by 2.5 mg each week to zero, or similar; Note: Patients who have used the above treatments in combination will not be required to be challenged with individual treatments as monotherapy AND

Drug Plan	Criteria for Restricted Benefit
	b) Immunosuppressive therapy as follows: - Azathioprine: minimum of 2 mg/kg/day for a minimum of 3 months; OR - 6-mercaptopurine: minimum of 1 mg/kg/day for a minimum of 3 months; OR - Methotrexate: minimum or 15 mg/week for a minimum of 3 months. OR - Immunosuppressive therapy discontinued at less than 3 months due to serious adverse effects or reactions. Applications for coverage must include information regarding the dosages and duration of trial of each treatment the patient received a description of any adverse effects, reactions, contraindications and/or lack of effect, as well as any other information requested by Alberta Blue Cross. Fistulising Crohn's Disease: Prior to initiation of infliximab therapy, New Patients must have actively draining perianal or enterocutaneous fistula(s) that have recurred or persisted despite: a) A course of an appropriate dose of antibiotic therapy (e.g. ciprofloxacin or metronidazole) for a minimum of 3 weeks; AND b) Immunosuppressive therapy: - Azathioprine: minimum of 2 mg/kg/day for a minimum of 6 weeks; OR - 6-mercaptopurine: minimum of 1 mg/kg/day for a minimum of 6 weeks; OR - Immunosuppressive therapy discontinued at less than 6 weeks due to serious adverse effects or reactions. [Note: Patients who have used the above treatments in combination for the treatment of Fistulising Crohn's will not be required to be challenged with individual treatments as monotherapy] Applications for coverage must include information regarding the dosages and duration of trial of each treatment the patient received a description of any adverse effects, reactions, contraindications and/or lack of effect, as well as any other information requested by Alberta Blue Cross. Coverage Criteria for Moderately to Severely Active Crohn's Disease AND/OR Fistulising Crohn's Disease - New Patients must meet the criteria above prior to being considered for approval. - All approvals are also subject to the following applicable criteria.

Drug Plan	Criteria for Restricted Benefit
	Induction Dosing for New Patients: - Coverage for Induction Dosing may only be approved for New Patients (those who have never been treated with infliximab by any health care provider). - 'Induction Dosing' means a maximum of one 5 mg/kg dose of infliximab per New Patient at each 0, 2 and 6 weeks (for a maximum total of three doses). - New Patients are eligible to receive Induction Dosing only once, after which time the Maintenance Dosing for New Patients and Continued Coverage for Maintenance Dosing criteria will apply. Maintenance Dosing: 'Maintenance Dosing' means one 5 mg/kg dose of infliximab per patient provided no more often than every 8 weeks for a period of 12 months to: - New Patients following the completion of Induction Dosing; OR - Existing Patients, who are patients that are being treated, or have previously been treated, with infliximab. Maintenance Dosing for New Patients after Completion of Induction Dosing: - The New Patient must be assessed by a Specialist between weeks 10 and 14 after the initiation of Induction Dosing to determine response by obtaining a Modified Harvey Bradshaw Index score for patients with Moderately to Severely Active Crohn's Disease and/or closure of individual fistulas as evidenced by no or minimal fistula drainage despite gentle finger compression of fistulas that were draining at baseline for Fistulising Crohn's; AND - The Specialist must confirm the Modified Harvey Bradshaw Index score shows a decrease from the New Patient's Baseline Score of greater than or equal to 3 points for patients with Moderately to Severely Active Crohn's and/or confirm closure of individual fistulas as evidenced by no or minimal fistula drainage despite gentle finger compression of fistulas that were draining at baseline for Fistulising Crohn's. Maintenance Dosing for Existing Patients: - The patient must be assessed by a Specialist at least 4 to 8 weeks after the day the last dose of infliximab was administered to the patient and prior to administration of the next dose to obtain: a Modified Harvey Bradshaw Index Score (Existing Patient's Baseline Score) for Moderately to Severely Active Crohn's and/or closure of individual fistulas as evidenced by no or minimal fistula drainage despite gentle finger compression of fistulas that were draining at baseline for Fistulising Crohn's; AND - these measures must be provided to Alberta Blue Cross for assessment for continued coverage for maintenance dosing. (For existing patients with Moderately to Severely Active Crohn's Disease with an incomplete response or for existing patients

Drug Plan	Criteria for Restricted Benefit
	with Fistulising Crohn's who respond then lose their response, the dose may be adjusted to 10 mg/kg by making an additional special authorization request to Alberta Blue Cross for the increased dose.) Continued Coverage for Maintenance Dosing: Continued coverage may be considered for one 5 mg/kg dose of infliximab per patient provided no more often than every 8 weeks for a period of 12 months, if the following criteria are met at the end of each 12 month period: - The New Patient or the Existing Patient must be assessed by a Specialist at least 4 to 6 weeks after the day the last dose of infliximab was administered to the patient and prior to the administration of the next dose to obtain a Modified Harvey Bradshaw Index Score for Moderately to Severely Active Crohn's and/or closure of individual fistulas as evidenced by no or minimal fistula drainage despite gentle finger compression of fistulas that were draining at baseline for Fistulising Crohn's; AND - For New Patients: The Specialist must confirm that the patient has maintained a greater than or equal to 3 point decrease from the New Patient's Baseline Score for Moderately to Severely Active Crohn's and/or closure of individual fistulas as evidenced by no or minimal fistula drainage despite gentle finger compression of fistulas that were draining at baseline for Fistulising Crohn's; OR - For Existing Patients: The Specialist must confirm that the patient has maintained the Existing Patient's Baseline Score and/or closure of individual fistulas as evidenced by no or minimal fistula drainage despite gentle finger compression of fistulas that were draining at baseline for Fistulising Crohn's. (For new and existing patients with Moderately to Severely Active Crohn's Disease with an incomplete response or for new and existing patients with Fistulising Crohn's who respond then lose their response, the maintenance dose may be adjusted to 10 mg/kg by making an additional special authorization request to Alberta Blue Cross for the increased dose.)" All requests (including renewal requests) for infliximab for Moderately to Severely Active Crohn's Disease and Fistulising Crohn's Disease must be completed using the Adalimumab for Crohn's/Infliximab for Crohn's/Fistulising Crohn's Disease Special Authorization Request Form (ABC 31200).
SK	Moderate to severe Crohn's Disease: -For treatment of patients who demonstrate continuing symptoms despite the use of optimal conventional therapies such as 5-ASA agents, glucocorticoids and immunosuppressive therapy. - For treatment of patients who are intolerant to conventional therapy including 5-ASA agents, glucocorticoids and immunosuppressive therapy.

Drug Plan	Criteria for Restricted Benefit
	Fistulising Crohn's Disease: - For treatment of patients with symptomatic enterocutaneous or perineal fistulae, enterovaginal fistulae or enterovesical fistulae (i.e. any type of fistulising Crohn's Disease). Clinical response should be assessed after the induction dose. Ongoing coverage will only be provided for those who respond to treatment. Patients undergoing this treatment should be reviewed every six months by a specialist in this area.
MB	For the treatment of moderate to severely active Crohn's Disease and/or Fistulising Crohn's Disease in patients refractory or with contraindications to an adequate course of 5- aminosalicyclic acid and corticosteroids and/or other immunosuppressive therapy. Request for coverage must be made by a physician who is a specialist in gastroenterology.
ON	Treatment of fistulising Crohn's Disease 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 Crohn's Disease is 5mg/kg/dose at 0, 2 and 6 weeks followed by 5mg/kg/dose every 8 weeks. Initial: 3 months First renewal: 1 year Second and subsequent renewals: 2 years
NB	- For moderately to severely active Crohn's disease in patients who are refractory or have contraindications to an adequate course of 5-aminosalicylic acid and corticosteroids and other immunosuppressive therapy. Initial approval will consist of 3 doses of 5 mg/kg given at weeks 0, 2 and 6. Clinical Note: - Infliximab will not be reimbursed in combination with other anti-TNF agents. Claim Notes: - Ongoing coverage for maintenance therapy will only be reimbursed for responders and for a dose not exceeding 5mg/kg every 8 weeks. Coverage must be reassessed annually and is dependent on evidence of continued response. - Must be prescribed by, or in consultation with, a gastroenterologist or physician with a specialty in gastroenterology
NS	For treatment of Crohn's disease in adults, when prescribed by a gastroenterologist or physician with a specialty in gastroenterology: - in patients with moderate to severe active disease refractory to 5-ASA products AND glucocorticoids (e.g., prednisone) AND immunosuppressive therapy (azathioprine or 6-mercaptopurine or methotrexate)**. Initial approval of infliximab will be for a

Drug Plan	Criteria for Restricted Benefit
	single infusion of 5mg/kg/dose. A second infusion may be warranted in patients not responding to the first infusion or in patients responding initially but then worsening before maintenance therapy is effective. Request for approval beyond induction therapy will be considered on a case-by-case basis - in patients with fistulising disease who have actively draining perianal or enterocutaneous fistula(e) that have recurred or persisted despite a course of appropriate antibiotic therapy (e.g., metronidazole +/-ciprofloxacin for a minimum of 3 weeks) AND immunosuppressive therapy (azathioprine or 6-mercaptopurine or methotrexate)**. Initial approval is for three infusions of infliximab of 5mg/kg/dose at 0, 2 and 6 week intervals **Patients who are very ill and not candidates for surgery may qualify for infliximab therapy without a trial of AZA, 6-MP or MTX, as they may require a more rapid onset of response
PE	For the treatment of moderate to severe Crohn=s Disease in patients who: 1. Have a Harvey Bradshaw Index score of 7 or more, AND 2. Have not responded to 5-ASA products (minimum trial of 3 grams per day for 6 weeks), AND 3. Have not responded to or are intolerant to glucocorticosteroid therapy (e.g. Prednisone) or where such therapy is contraindicated, AND 4. Have not responded to or are intolerant to immunosupressive therapy (Azathioprine, Mercaptopurine or Methotrexate) or where such therapy is contraindicated. Initial approval for Infliximab will allow for 3 doses of 5mg/kg/dose administered at 0, 2, and 6 weeks. Renewal of coverage will require reassessment of the patient and submission of a new Crohn=s Disease Special Authorization form. Continued coverage will be approved at a dose not exceeding 5mg/kg every 8 weeks For the treatment of fistulising Crohn's Disease in patients who: 1. Have a Harvey Bradshaw Index score of 7 or more, AND 2. Have an actively draining perianal or enercutaneious fistula(e) that have recurred or persisted despite a course of appropriate antibiotic therapy (e.g. Ciprofloxacin with or without Metronidazole for a minimum of 3 weeks), AND 3. Have not responded to or are intolerant to immunosupressive therapy (Azathioprine, Mercaptopurine or Methotrexate) or where such therapy is contraindicated. Initial approval for Infliximab will allow for 3 doses of 5mg/kg/dose administered at 0, 2, and 6 weeks. Renewal of coverage will require reassessment of the patient and submission of a new Crohn's Disease Special Authorization form. Continued coverage will be approved at a dose not exceeding 5mg/kg every 8 weeks.
NL	For the treatment of patients with moderate or severe active disease* with contraindications to or not achieving remission with glucocorticosteroids AND immunosuppressive therapy.

Drug Plan	Criteria for Restricted Benefit
	Initial request must include current Crohn's Disease Activity Index (CDAI) or the Harvey-Bradshaw Index Assessment (HBI) score. Initial approval, 3 infusions of infliximab 5mg/kg at week 0, 2 & 6. Continued coverage dependent on evidence of response using criteria such the 100 point reduction in Crohn's Disease Activity Index (CDAI) or the Harvey-Bradshaw Index Assessment (HBI) with a score of 5 or less or a decrease in score of 4 or more. Coverage can be reassessed annually dependent on evidence of response (as outlined above) The maximum approved dose is 5mg/kg every 8 weeks. * Patients very ill & not candidates for surgery may qualify for immediate infliximab induction therapy, as they may require a more rapid response. Concurrent use of biologics not approved. Written request by Gastroenterologist or physician with a specialty in gastroenterology
YK	For moderate to severely active Crohn's Disease on recommendation of a specialist. Consult to be provided. For patients with a current Harvey Bradshaw Index (HBI) >7, who are intolerant or refractory to 5-ASA (3 g daily for at least 6 weeks) AND are refractory, intolerant or dependant on glucocorticoids, AND who are refractory or intolerant to at least one of azathioprine, 6-mercaptopurine or methotrexate after a 3 month trial. For fistulising Crohn's Disease on recommendation of a specialist. Consult to be provided. For patients with actively draining fistula(s) despite a 3 week trial of ciprofloxacin or metronidazole, AND at least a 6 week trial of azathioprine or 6-mercaptopurine
NT	Fistulising Crohn's disease according to established criteria. -For adult patients with moderately to severely active Crohn's Disease who have had an inadequate response to conventional therapy. For the treatment of FISTULIZING CROHN'S DISEASE Criteria for initial for one year: - Prescribed by a gastroenterology specialist The initial coverage will allow for 3 doses of 5mg/kg/dose, administered at 0, 2 and 6 weeks. For continued coverage, patient must be reassessed after the initial doses. Patient meets all the following criteria: -Patient is an adult with actively draining perianal or entercutaneous fistula(e) that have recurred or persisted despite: -a course of appropriate antibiotic therapy (e.g. ciprofloxacin with or without metronidazole for a minimum of 3 weeks) PLUS -immunosuppressive therapy:

Drug Plan	Criteria for Restricted Benefit
	-azathioprine 2 to 2.5mg/kg/day for a minimum of 6 weeks or treatment discontinued before 6 weeks due to severe adverse reactions. OR -6-mercaptopurine, 50-70mg/day for a minimum of 6 weeks or treatment discontinued before 6 weeks due to severe adverse reactions. OR For the treatment for SEVERE ACTIVE CROHN`S DISEASE Criteria for initial for one year: -Prescribed by a gastroenterology specialist The initial coverage will allow for 3 doses of 5mg/kg/dose, administered at 0, 2 and 6 weeks. For continued coverage, patient must be reassessed after the initial doses. Patient meets the following criteria: Patient is an adult with severe active Crohn's disease that has recurred or persisted despite: -Therapy with 5-ASA products (at least 3g/day for a minimum of 6 weeks). PLUS -Glucocorticoids equivalent to prednisone 40mg/day for a minimum of 2 weeks. OR -Treatment discontinued due to serious adverse reactions OR OR -Contraindication to glucocorticoid therapy. PLUS -Azathioprine 2 to 2.5mg/kg/day for a minimum of 3 months. OR -6-mercaptopurine 50 to 70mg/day for a minimum of 3 months. OR -Methotrexate 15 to 25mg/week for a minimum of 3 months.
NIHB	Fistulising Crohn's disease according to established criteria. -For adult patients with moderately to severely active Crohn's Disease who have had an inadequate response to conventional therapy. For the treatment of FISTULIZING CROHN'S DISEASE Criteria for initial for one year:

Drug Plan	Criteria for Restricted Benefit
	- Prescribed by a gastroenterology specialist The initial coverage will allow for 3 doses of 5mg/kg/dose, administered at 0, 2 and 6 weeks. For continued coverage, patient must be reassessed after the initial doses. Patient meets all the following criteria: -Patient is an adult with actively draining perianal or entercutaneous fistula(e) that have recurred or persisted despite: -a course of appropriate antibiotic therapy (e.g. ciprofloxacin with or without metronidazole for a minimum of 3 weeks) PLUS -immunosuppressive therapy: -azathioprine 2 to 2.5mg/kg/day for a minimum of 6 weeks or treatment discontinued before 6 weeks due to severe adverse reactions. OR -6-mercaptopurine, 50-70mg/day for a minimum of 6 weeks or treatment discontinued before 6 weeks due to severe adverse reactions. For the treatment for SEVERE ACTIVE CROHN`S DISEASE Criteria for initial for one year: -Prescribed by a gastroenterology specialist The initial coverage will allow for 3 doses of 5mg/kg/dose, administered at 0, 2 and 6 weeks. For continued coverage, patient must be reassessed after the initial doses. Patient meets the following criteria: Patient is an adult with severe active Crohn's disease that has recurred or persisted despite: -Therapy with 5-ASA products (at least 3g/day for a minimum of 6 weeks). PLUS -Glucocorticoids equivalent to prednisone 40mg/day for a minimum of 2 weeks. OR -Treatment discontinued due to serious adverse reactions OR OR -Contraindication to glucocorticoid therapy. PLUS -Azathioprine 2 to 2.5mg/kg/day for a minimum of 3 months. OR -6-mercaptopurine 50 to 70mg/day for a minimum of 3 months. OR

Drug Plan	Criteria for Restricted Benefit
	-Methotrexate 15 to 25mg/week for a minimum of 3 months.
DND	Crohn's Disease: - when prescribed by a gastroenterologist for patients with moderate to severe Crohn's Disease who are refractory or intolerant to: - 5-ASA products at 3g/day for 6 weeks AND prednisone 40mg/day for 2 weeks AND Immunosuppressive therapy as follows: - azathioprine 2-2.5mg/kg/day for 3 months OR - mercaptopurine 50-75mg/day for 3 months OR - methotrexate 15-25mg/week for 3 months OR - Immunosuppressive therapy discontinued at less than 3 months due to serious adverse effects or reactions Fistulising Crohn's: - when prescribed by a gastroenterologist for patients with active draining fistulas despite: - ciprofloxacin + metronidazole for 3 weeks AND - azathioprine for a minimum of 6 weeks OR - 6-mercaptopurine for 6 weeks
VAC	Criteria Not Publically Available via VAC Website

Restricted Benefit Criteria for REMICADE® for the treatment of Ulcerative Colitis

Drug Plan	Criteria for Restricted Benefit
BC	Not a Benefit
AB	Special authorization coverage may be provided for the reduction in signs and symptoms and induction and maintenance of clinical remission of Ulcerative Colitis in adult patients (18 years of age or older) with active disease (characterized by a partial Mayo score >4 prior to initiation of biologic therapy) and who are refractory or intolerant to: - mesalamine: minimum of 4 grams/day for a minimum of 4 weeks AND - corticosteroids (failure to respond to prednisone 40 mg daily for 2 weeks, or; steroid dependent i.e. failure to taper off steroids without recurrence of disease or disease requiring a second dose of steroids within 12 months of previous dose). 'Refractory' is defined as lack of effect at the recommended doses and for duration of treatments specified above. 'Intolerant' is defined as demonstrating serious adverse effects or contraindications to treatments as defined in product monographs. Immunosuppressive therapy as follows may also be initiated if in the clinician's judgment a trial is warranted: i) Azathioprine: minimum of 2 mg/kg/day for a minimum of 2 months; OR ii) 6-mercaptopurine: minimum of 1 mg/kg/day for a minimum of 2 months For coverage, this drug must be prescribed by a Specialist in Gastroenterology or a physician appropriately trained by the University of Alberta or the University of Calgary and recognized as a prescriber by Alberta Blue Cross ('Specialist'). Initial coverage may be approved for three doses of 5 mg/kg of infliximab at 0, 2 and 6 weeks. -Patients will be limited to receiving a one dose of infliximab per prescription at their pharmacy. - Patients will be permitted to switch from one biologic agent to another following an adequate trial of the first biologic agent if unresponsive to therapy, or due to serious adverse effects or contraindications. An adequate trial is defined as at a minimum the completion of induction dosing (e.g. initial coverage period). - Patients will not be permitted to switch back to a previously trialed biologic agent if they were deemed unresponsive to therapy. - Patients are limited to receiving one biologic agent at a time regardless of the condition for which it is being prescribed. For continued coverage beyond three doses, the patient must meet the following criteria: 1) The patient must be assessed by a Specialist between weeks 10 and 14 after the initiation of therapy to determine response. 2) The Specialist must confirm in writing that the patient is a 'responder' that meets the following criteria: - a decrease in the partial Mayo score of greater than or equal to 2 points Following this assessment, continued coverage may be approved for dose of 5 mg/kg every 8 weeks for a period of 12 months. Ongoing coverage may be considered only if the following criteria are met at the end of each 12-month period: 1) The patient has been assessed by a Specialist in Gastroenterology to determine response;

Drug Plan	Criteria for Restricted Benefit
	2) The Specialist must confirm in writing that the patient has maintained a response to therapy as indicated by: - a decrease in the partial Mayo score of greater than or equal to 2 points from the score prior to initiation of infliximab therapy Note: For patients who showed a response to induction therapy then experienced secondary loss of response while on maintenance dosing with 5 mg/kg, the maintenance dose may be adjusted from 5 mg/kg to 10 mg/kg by making an additional special authorization request to Alberta Blue Cross for the increased dose. All requests (including renewal requests) for infliximab for Ulcerative Colitis must be completed using the Infliximab for Ulcerative Colitis Special Authorization Request Form (ABC 60008).
SK	For treatment of ulcerative colitis in patients unresponsive to high dose intravenous steroids. NOTE: Clinical response should be assessed after the three-dose induction phase before proceeding to maintenance therapy. Ongoing coverage will only be provided for those who respond to therapy. Patients undergoing this treatment should be reviewed every six months by a specialist in this area. 3) Adequate response to treatment assessed at 12 weeks defined as at least 50% reduction in pre-treatment baseline BASDAI score or by > 2 units AND a reduction of > 2cm in the spinal pain VAS. NOTE: Coverage will not be provided when a patient switches to another anti-TNF agent if the patient fails to respond or if there is a loss of response to the first agent. Requests for coverage for this indication must be made by the rheumatologist. A second application would also be required after 12 weeks to assess and would need to show an improvement to the patient's condition on either of these medications. Please refer to the Formulary website for the application form. Subsequent annual renewal requests (beyond 15 months) will be considered for patients whose BASDAI scores do not worsen (i.e. remains within two points of the second assessment). For all of the above indications this product should be used in consultation with a specialist in this area. (h) For treatment of ulcerative colitis in patients unresponsive to high dose intravenous steroids. NOTE: Clinical response should be assessed after the three-dose induction phase before proceeding to maintenance therapy. Ongoing coverage will only be provided for those who respond to therapy. Patients undergoing this treatment should be reviewed every six months by a specialist in this area
MB	For the treatment of patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy including 5-aminosalicylate compounds corticosteroids and immunomodulators. Request for coverage must be made by a physician who is a specialist in gastroenterology
ON	Induction 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

Drug Plan	Criteria for Restricted Benefit
	2. Moderate disease a. Mayo score between 6 and 10 (inclusive) AND b. *Endoscopic subscore of 2 AND c. Failed 2 weeks of oral prednisone ≥ 40mg (or IV equivalent for at least 1 week) AND 3 months of Azathioprine (AZA)/ 6-Mercaptopurine (6MP) (or where the use of immunosuppressants is contraindicated) OR d. Stabilized with 2 weeks of oral prednisone ≥ 40mg (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 subscore ≥ 2 c. Failed 2 weeks of oral prednisone ≥ 40mg (or 1 week IV equivalent) OR d. Stabilized with 2 weeks of oral prednisone ≥ 40mg (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) *The endoscopy procedure must be done within the last year but does not have to be full endoscopy. Maintenance Criteria: 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

Drug Plan	Criteria for Restricted Benefit
NB	Not a Benefit
NS	Not a Benefit
PE	Not a Benefit
NL	Not a Benefit
YK	For Ulcerative Colitis on recommendation of a specialist. Consult to be provided. For patients with a Mayo score >6 AND an endoscopic subscore ≥ 2 (within last 12 months AND failed 2 weeks of oral prednisone ≥ 40mg (or 1 week IV equivalent) AND 3 months of azathioprine or 6-mercaptopurine OR stabilized on prednisone as above but the prednisone dose cannot be tapered despite 3 months of DMARDS. Only one month's dose to be dispensed at a time. Approval for 12 month period
NT	Not a Benefit
NIHB	Not a Benefit
DND	Not a Benefit
VAC	Not a Benefit

APPENDIX 3: SUMMARY OF PATIENT INPUT

1. Description of Patient Groups Supplying Input:
Two patient groups provided input for this submission: The Gastrointestinal (GI) Society and Crohn's and Colitis Canada (CCC).

The mission of the GI Society is to provide evidence-based information on conditions related to the GI tract and liver, improve the lives of people living with these conditions, support research, advocate for health care access, and promote GI and liver health. The GI Society provides pamphlets and online information, delivers lectures, and responds to information requests from patients and health care professionals. English (www.badgut.org) and French (www.mauxdeventre.org) websites are available. Financial contributions are received from pharmaceutical companies (Pfizer, AbbVie Corporation, Actavis, AstraZeneca Canada Inc., Innovative Medicines Canada, Ferring Inc., Gilead Sciences Canada Inc., GlaxoSmithKline Inc., Janssen Canada, Merck Canada Inc., Pfizer Canada Inc., Shire Canada Inc., and Takeda Canada Inc.), governments, foundations, and individuals. No conflict of interest was declared in preparing the patient input for this submission.

CCC is a national, volunteer-based charity that works on finding cures for Crohn's disease (CD) and ulcerative colitis (UC), improving the lives of people living with these conditions, providing patient programs, advocating on behalf of patients, and increasing awareness. It is among the foremost charity funders of inflammatory bowel disease (IBD) research in the world. The organization has chapters in 45 communities across Canada. During 2014-2015, 11% of CCC's revenues were from corporate donations. Major supporters were: AbbVie Corporation, Janssen Inc., The Leona M. and Harry B. Helmsley Charitable Trust, M&M Meat Shops, Takeda Canada Inc., and Vertex Pharmaceuticals (Canada) Inc. No conflict of interest was declared in preparing the patient input for this submission.

2. Condition Related Information:
The CCC obtained information from CCC published reports, CCC surveys, and educational brochures available on the organization's website (www.crohnsandcolitis.ca). The sources of information consulted by the GI Society were not provided.

The GI Society indicated that there are differences between UC and CD with respect to the extent and areas of inflammation experienced by patients with these conditions. The inflammation of CD affects more areas of the intestinal tract and is deeper in extent compared with UC. In addition to GI symptoms, patients with either UC or CD may experience extra-intestinal manifestations, such as fever, inflammation of eyes or joints, ulcers of mouth or skin, tender and inflamed nodules on the shins, anxiety, and stress. Symptoms may have profound effects on the physical, social, and emotional aspects of patients' lives. Patients also report being constantly concerned about disease flare-ups, which may be worse in severity compared with previous flares and occur unpredictably. This causes great disruption to patients' lives. Sustained remission or treatment response, therefore, is desired by patients.

The CCC reported that the most unbearable symptoms experienced by patients are lack of control over bowel movements and urgent and frequent need to use the bathroom. A CCC 2011 survey found that 73% of patients experienced 5 to 20 or more bowel movements per day. Although patients indicated blood in the stool and abdominal pain as important symptoms, the dominating concern was access to a washroom. Some patients were also concerned about the increased risk of colon cancer. Limitations in

leisure activities (e.g., going out for dinners, movies, and concerts), physical activities, use of public transportation, and work were reported. According to one respondent, "You simply can't lead a normal life of working and going to the office." Thirty-four per cent frequently missed playing sports, 22% missed school trips, 20% skipped family vacations, 40% avoided parties, and 22% did not attend special events such as graduations or family weddings. In addition, patients reported experiencing greater scrutiny from bosses due to frequent washroom breaks or sick days. IBDs are attached with stigma, which makes it difficult for patients to openly talk about their condition. Caregivers are also affected by the condition, often acting as advocates for their loved one and devoting time and resources to help manage the potential limitations in carrying out day-to-day activities. The process of caring, however, may affect the caregiver's mental and physical health, and often exerts financial burden including out-of-pocket expenses associated with disease management.

3. Current Therapy-Related Information:
The CCC obtained information from patient reports of innovator drugs, which were included in previous drug submissions to CADTH. The sources of information consulted by the GI Society were not provided. A survey was conducted by the GI Society in 2015 on their English and French websites to understand the perspectives of patients with IBD or caregivers of a person with IBD regarding subsequent entry biologics (SEBs). A total of 423 respondents participated, from all provinces and territories.

The goals of therapy are induction of remission and maintenance of remission. This is achieved by using treatments that control inflammation in the intestinal tract. Older treatments include 5-aminosalicylic acid (5-ASA), corticosteroids, and immunosuppressive drugs. According to the GI Society, the introduction of biologic drugs was life-changing and "revolutionary" when older treatments failed to achieve the goals of therapy. However, biologics do have side effects and risks and, therefore, are prescribed only if they are the best option for controlling inflammation. The course of IBD is often unpredictable and unique among patients and, thus, treatment must be individualized; a treatment regimen that works for one patient may not be suitable for another. Availability and choice of different treatments options are a must. Since there is no cure for IBD, is it important to maintain ongoing medical care, proper nutrition, and medication.

Patients who reported to the CCC indicated that they responded well to the innovator biologic. After failure of first-line treatments, innovator biologic drugs have allowed patients to achieve remission and experience a reduction in the number of bowel movements, decreased fatigue, less pain, and less psychological stress associated with need for washroom access. According to one respondent, "with steroids I was at 60% but with [innovator biologics] I'm at 95%." Patients reported that innovator biologics helped them achieve as close to a normal life as possible. Biologic drugs offer an alternative to surgery when other treatments have failed. This prevents the complications of surgery, such as continence/soiling, poor pouch function, pouchitis, sexual dysfunction, and loss of fertility in females.

4. Expectations for the Drug Being Reviewed:
The information for this section was obtained from the survey conducted by the GI society.

Patients expect that treatment will improve their quality of life, which means relief of symptoms, alleviation of anxiety and stress, ability to lead a normal life with family, career/education, and without interruptions due to flare-ups. They expect that an approved SEB has been proven to be safe and effective, specifically in IBD.

Patients expressed concerns about the safety and efficacy of SEBs, the regulatory process of SEBs in Canada, and switching between innovator and SEB treatments, especially without their consent. They do not want cost to be the only consideration when deciding which biologic to use. In addition, it was important for patients that the physician chooses in consultation with them the best drug for their condition (and that the choice is not just made by a government or drug plan). Patients expect that SEB regulations consider, in order of priority: safety, a review and approval process that is as rigorous as for the innovator, that the SEB is tested for all indications/diseases, the importance of more treatment options, and that the SEB is clinically tested in Canadians.

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