CADTH

CADTH Biosimilar Summary Dossier

BEVACIZUMAB (MVASI)

(Amgen Canada Inc.)

Indication(s): Metastatic Colorectal Cancer / Non-Small Cell Lung Cancer Biosimilar

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Section 1: Biosimilar Product Information

Biosimilar (Brand Name)	MVASI™
Active Pharmaceutical Ingredient	Bevacizumab
Manufacturer	Amgen Canada Inc.
Strength(s) / Dosage Form(s) / Route(s) of Administration[a]	100 mg and 400 mg vials (25 mg/mL solution for injection); intravenous (IV) infusion
Health Canada–Approved Indication(s) (or Anticipated Indications)	**Metastatic Colorectal Cancer (mCRC)** MVASI™, in combination with fluoropyrimidine-based chemotherapy, is indicated for first-line treatment of patients with metastatic carcinoma of the colon or rectum. Consideration should be given to current standard of care guidelines for colorectal cancer. **Locally Advanced, Metastatic or Recurrent Non-Small Cell Lung Cancer (NSCLC)** MVASI™, in combination with carboplatin/paclitaxel chemotherapy regimen, is indicated for treatment of patients with unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer.
Health Canada–Approved Reference Product Indications Not Being Sought by the Manufacturer (if Applicable)	Amgen is choosing not to seek these indications: • Platinum-Sensitive Recurrent Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer; • Platinum-Resistant Recurrent Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer
NOC Date(s) (or Anticipated NOC Date[s])[b]	April 30, 2018

NOC = notice of compliance.
[a] Please provide all applicable strength(s)/Dosage Form(s)/Route of Administration, as applicable.
[b] Please provide NOC date(s) according to indication.

Section 2: Reference Product Information

Reference Product (Brand Name)	Avastin®
Active Pharmaceutical Ingredient	Bevacizumab
Manufacturer	Hoffmann-La Roche Ltd
Strength(s) / Dosage Form(s) / Route(s) of Administration	100 mg and 400 mg vials (25 mg/mL solution for injection); intravenous (IV) infusion
Health Canada–Approved Indication(s)	**Metastatic Colorectal Cancer (mCRC)** Avastin® in combination with fluoropyrimidine-based chemotherapy is indicated for first-line treatment of patients with metastatic carcinoma of the colon or rectum. **Locally Advanced, Metastatic or Recurrent Non-Small Cell Lung Cancer (NSCLC)** Avastin®, in combination with carboplatin/paclitaxel chemotherapy regimen, is indicated for treatment of patients with unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer. **Platinum-Sensitive Recurrent Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer** Avastin®, in combination with carboplatin and gemcitabine is indicated for the treatment of patients with first recurrence platinum-sensitive epithelial ovarian, fallopian tube, or primary peritoneal cancer. These patients should not have received prior vascular endothelial growth factor (VEGF)-targeted therapy including Avastin®. **Platinum-Resistant Recurrent Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer** Avastin® in combination with paclitaxel, topotecan or pegylated liposomal doxorubicin is indicated for the treatment of patients with recurrent, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens. These patients should not have received prior VEGF-targeted therapy including Avastin®. **Malignant Glioma (WHO Grade IV) - Glioblastoma** Avastin®, in combination with lomustine, is indicated for the treatment of patients with glioblastoma after relapse or disease progression, following prior therapy.

Section 3: Manufacturer's Reimbursement Request

Manufacturer's Reimbursement Request and Rationale	Request that MVASI™ be reimbursed in a manner similar to Avastin®, in keeping with the Health Canada-approved indications for MVASI™ which include: **Metastatic Colorectal Cancer (mCRC)** MVASI™, in combination with fluoropyrimidine-based chemotherapy, is indicated for first-line treatment of patients with metastatic carcinoma of the colon or rectum. Consideration should be given to current standard of care guidelines for colorectal cancer. **Locally Advanced, Metastatic or Recurrent Non-Small Cell Lung Cancer (NSCLC)** MVASI™, in combination with carboplatin/paclitaxel chemotherapy regimen, is indicated for treatment of patients with unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer. Note, this is not an offer for sale. MVASI is not currently available commercially in Canada.

Section 4: Health Canada's Assessment of MVASI™ for Market Authorization

4.1 Authorized Indications

Indications: Indications have been granted on the basis of similarity between MVASI™ and the reference biologic drug, Avastin®. Further details can be found in the Health Canada–approved product monographs for MVASI™ and Avastin®:

- MVASI™: https://pdf.hres.ca/dpd_pm/00045004.PDF
- Avastin®: https://pdf.hres.ca/dpd_pm/00045825.PDF

Authorization of Indications (if Applicable): Randomized clinical trials have not been conducted to compare MVASI™ to Avastin® in patients with metastatic colorectal cancer. Based on the totality of evidence derived from the comparative structural, analytical and functional, non-clinical, pharmacokinetic (PK) and clinical data, similarity between MVASI™ and Avastin® has been demonstrated. To further support the authorization of MVASI™ in each of the claimed indications, scientific rationale that was in line with Health Canada's biosimilar guidance document was provided. Based on the assessment of all the relevant data provided in the Health Canada submission, the benefit risk balance of MVASI™ is considered favourable for the treatment of locally advanced, metastatic or recurrent non-squamous NSCLC and mCRC.

4.2 Summary of Comparative Clinical Trials

4.2.1 Comparative Clinical Trial Design and Patient Demographics

The clinical program for MVASI™ (ABP 215) consisted of 2 key studies conducted using subjects and endpoints capable of detecting any clinically meaningful differences between MVASI™ and the reference biologic drug Avastin®.

- A randomized, single-blind, 3-arm, parallel group pharmacology study (Study 20110216) in 202 healthy adult male subjects demonstrated the bioequivalence of MVASI™ following a single 3 mg/kg intravenous (IV) infusion relative to that from 3 mg/kg IV infusion of Avastin® sourced from the United States (US) and European Union (EU).[1]
- The clinical equivalence of MVASI™ to Avastin® was demonstrated in a randomized, double-blind, active-controlled phase 3 trial (Study 20120265) based on the risk ratio of objective response rate (ORR) in 642 subjects with stage IV or recurrent metastatic non-squamous NSCLC receiving first-line chemotherapy with carboplatin and paclitaxel.[2-4]

An overview of the trial designs and demographic characteristics of patients enrolled in each clinical study are presented in Table 1.

Table 1: Comparative Clinical Trial Design and Patient Demographics

Study Number	Trial Design	Patient Population	Dosage, Route of Administration, and Duration	Number of Subjects or Patients	Sex
20110216	Randomized, single-blind, single-dose, 3-arm, parallel-group study in healthy adult male subjects	Healthy men, 18-45 years of age with BMI between 18 and 30 kg/m^2	Single dose of 3 mg/kg MVASI or 3 mg/kg Avastin (sourced from either the US or the EU) via IV infusion over 90 min	202 subjects were randomized: MVASI n=68; Avastin (US) n=67; Avastin (EU) n=67	Male: 202 (100%)
20120265	Randomized, double-blind, active-controlled phase 3 study in adult subjects with non-squamous non-small cell lung cancer (NSCLC)	Adults with stage 4 or recurrent metastatic non-squamous NSCLC receiving first-line carboplatin/paclitaxel chemotherapy	MVASI 15 mg/kg Q3W with IV carboplatin (AUC of 6) and paclitaxel (200 mg/m^2); Avastin 15 mg/kg Q3W with IV carboplatin (AUC of 6) and paclitaxel (200 mg/m^2); Both treatment arms, doses were administered as an IV infusion Q3W (±7 days) for 6 cycles.	642 patients were randomized: MVASI n=328; Avastin n=314	Male: 384 (59.8%)

AUC = area under the serum concentration-time curve; BMI = body mass index, SD = standard deviation.

4.2.2 Comparative Clinical Trial Results

Comparative Pharmacokinetic Study 20110216

Results from PK analyses in Study 20110216 demonstrated that the 90% confidence intervals (CIs) for the ratios of geometric means for the parameters C_{max}, AUC from time 0 extrapolated to infinity (AUC_{inf}), and area under the serum concentration-time curve from time 0 to time of last quantifiable concentration (AUC_{last}) were fully contained within the standard prespecified criteria of 0.80 to 1.25, confirming PK similarity with each pairwise comparison (Table 2).[1] The bioequivalence of MVASI™ relative to Avastin® (US) and Avastin® (EU) was demonstrated. The PK parameters of MVASI™ and the EU sourced Avastin® (the designated Canadian reference biologic drug) are summarized in Table 2.

Table 2: Summary of MVASI™ and Avastin® (EU) Pharmacokinetic Parameters (Study 20110216)[1]

Parameter (unit)	MVASI™	Avastin® (EU)	Ratio of adjusted LS geometric means (90% CI)
AUC_{last} (µg h/mL), GM [n]	28200 [62]	29400 [64]	0.96 (0.92-1.00)
AUC_{Inf} (µg h/mL), GM [n]	29400 [66]	30600 [66]	0.96 (0.92-1.01)
C_{max} (µg/mL), GM [n]	87.2 [67]	84.7 [64]	1.03 (0.98-1.08)
t_{max} (h), median [n] (min-max)	1.50 [67] (1.47-24.0)	3.94 [64] (1.47-8.00)	
$t_{½}$ (days), mean [n] (SD)	17.7 [66] (3.68)	18.5 [66] (3.28)	

AUC_{inf} = area under the serum concentration curve from time 0 extrapolated to infinity; AUC_{last} = AUC from time 0 to the last quantifiable concentration; C_{max} = maximum observed concentration; CI = confidence interval; GM = geometric mean; LS = least squares; n = number of subjects with evaluable parameters; SD = standard deviation.

The results of this phase 1 study demonstrated that single doses of MVASI™ and Avastin® administered to healthy subjects were safe and well tolerated. All 202 subjects received investigational product: 11 (5.4%) subjects discontinued from the study prematurely, none due to adverse events. The incidence of adverse events (AEs) was 57.6% and 61.2% in the MVASI™ and Avastin® (EU) groups, respectively, while the incidence of AEs was slightly lower in the US site (37.1% MVASI™; 32.8% Avastin® (US). No subjects tested positive for anti-drug antibodies (ADAs). No new safety signals with regard to treatment with MVASI™ were identified.[1]

Comparative Safety and Efficacy Study 20120265

Study 20120265, a phase 3, randomized, active-controlled study conducted in subjects with non-squamous NSCLC, supports the clinical equivalence of efficacy between MVASI™ and Avastin®. The NSCLC population was chosen because this population is sensitive to detect any clinically meaningful difference between the products if it exists. The determination of similarity in efficacy was based on accepted and sensitive measures of disease activity for NSCLC. The primary efficacy endpoint was the risk ratio (RR) of the objective response rate (ORR) as defined by RECIST version 1.1.[5] ORR is a direct and objective measure of antitumour activity and is predictive of progression-free survival (PFS) and overall survival.[6] ORR is considered a sensitive endpoint to evaluate the efficacy of MVASI™ compared with Avastin® in the NSCLC population based on past clinical studies with bevacizumab.

As shown in Table 3, the ORR based on the central, independent, blinded radiologists' review was 39.0% and 41.7% in the MVASI™ and Avastin® treatment arms, respectively, in the intent-to-treat population. Clinical equivalence of the primary endpoint was demonstrated by comparing the 2-sided 95% CI of the risk ratio of ORR between the treatment arms. The risk ratio of 0.93 (95% CI: 0.77, 1.12) was well within the prespecified equivalence margin (95% CI: 0.67, 1.5). Secondary efficacy endpoint results with regards to duration of response and progression-free survival (PFS) also confirm similarity of efficacy between MVASI™ and Avastin® treatment groups.

Table 3: Summary of Objective Response Rate, Duration of Response, and Progression-Free Survival of MVASI™ and Bevacizumab (ITT Population) (Study 20120265)[2,3]

Parameter (unit)	MVASI™ (N = 328)	Avastin® (N = 314)
Primary Efficacy Endpoint:		
ORR[a], n (%)	128 (39.0)	131 (41.7)
RR for ORR (MVASI/bevacizumab)[b]	0.93 (95% CI: 0.77, 1.12)	
Secondary Efficacy Endpoints:		
RD for ORR[b], (%)	-2.90% (95% CI: -10.48%, 4.67%)	
Duration of response (months), median	5.8	5.6
Subjects with disease progression or death, n (%)	131 (39.9%)	125 (39.8%)
PFS (months), median	6.6	7.9
HR[c]	1.03 (95% CI: 0.80, 1.34)	

CI = confidence interval; HR = hazard ratio; ORR = objective response rate; PFS = progression-free survival; RD = risk difference; RR = risk ratio.

[a] Objective response rate was defined as the percentage of subjects with an objective response. Objective response was defined as a best overall response of partial response or complete response as defined by RECIST v1.1.

[b] Point estimate and CI have been estimated using a generalized linear model adjusted for the randomization stratification factors geographic region, ECOG performance status, and sex.

[c] HR for MVASI relative to bevacizumab, based on a stratified Cox proportional hazards model. Stratification factors are geographic region, ECOG performance status, and sex.

Safety and Immunogenicity

MVASI™ was similar to Avastin® with respect to clinical safety (Table 4). The incidence of AEs was similar between the treatment arms and was within the expected range of incidence and severity described for the reference product Avastin®. There were no

clinically meaningful differences in overall survival (OS) between MVASI™ and Avastin® treatment groups: 43 (13.3%) and 36 (11.7%) died before the end of the study, respectively.

Immmunogenicity was evaluated in study 20120265 at baseline, week 7, week 13, and week 19. An electrochemiluminescent (ECL) immunoassay was used to detect antibodies capable of binding MVASI™ or Avastin®. During the study, 4 of 294 (1.4%) evaluable subjects in the MVASI™ arm and 7 of 284 (2.5%) evaluable subjects in the Avastin® arm developed binding ADAs. Among the subjects with positive binding ADAs, no subjects tested positive for neutralizing antibodies. There were no clinically meaningful differences in immunogenicity between MVASI™ and Avastin®.

Table 4: Summary of Adverse Events (Safety Analysis Population) (Study 20120265)[3]

Adverse event, n (%)	MVASI™ (N = 324)	Avastin® (N = 309)
Any grade ≥ 3 TEAE	139 (42.9)	137 (44.3)
Any fatal TEAE	13 (4.0)	11 (3.6)
Any serious TEAE	85 (26.2)	71 (23.0)
Any TEAE leading to discontinuation of IP	61 (18.8)	53 (17.2)

IP = investigational product; TEAE = treatment-emergent adverse event.
Note: For each category, subjects are included only once, even if they had multiple events in that category.

Section 5: Cost Overview

5.1 Cost Comparison

MVASI™ (bevacizumab) is being submitted at an approximately 25% price discount relative to the current Ontario list price of the reference product Avastin® (bevacizumab). The cost differential equates to $133.23 per 100 mg vial or $1.33230 per mg. MVASI™ is also available in a 400 mg vial and will be priced equally on a per mg basis.

Expected savings may vary among public drug plans. The cost of treatment with MVASI™ should provide significant cost savings for jurisdictions compared with the cost of treatment with Avastin®.

Table 5: Cost Comparison of MVASI™ and Avastin® for Metastatic Colorectal Cancer (mCRC)

Drug / Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Drug Cost ($)
Canadian Costs					
MVASI™	25 mg/mL	Solution for injection	$385.94 per 100 mg vial; $1,543.77 per 400 mg vial[a]	5mg/kg of body weight once every 14 days[b]	$1,350.79[e]
Avastin®	25 mg/mL	Solution for injection	$519.17 per 100 mg vial; $2,076.71 per 400 mg vial[c]	5mg/kg of body weight once every 14 days[d]	$1,817.10[e]

[a] Submitted price of MVASI.
[b] MVASI Product Monograph, 30 April 2018, Amgen Canada Inc.
[c] List price for Ontario *(Source: DeltaPA, IQVIA)*.
[d] Avastin Product Monograph, 06 June 2018, Hoffmann-LaRoche Limited.
[e] Cost per 14-day course at the recommended weight-based dose, assuming a body weight of 70 kg, and does not include wastage.

Table 6: Cost Comparison of MVASI™ and Avastin® for Non-Small Cell Lung Cancer (NSCLC)

Drug / Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Drug Cost ($)
Canadian Costs					
MVASI™	25 mg/mL	Solution for injection	$385.94 per 100 mg vial; $1,543.77 per 400 mg vial[a]	15mg/kg of body weight once every 3 weeks[b]	$4,052.37[e]
Avastin®	25 mg/mL	Solution for injection	$519.17 per 100 mg vial; $2,076.71 per 400 mg vial[c]	15mg/kg of body weight once every 3 weeks[d]	$5,451.29[e]

[a] Submitted price of MVASI.
[b] MVASI Product Monograph, 30 April 2018, Amgen Canada Inc.
[c] List price for Ontario *(Source: DeltaPA, IQVIA)*.
[d] Avastin Product Monograph, 06 June 2018, Hoffmann-LaRoche Limited.
[e] Cost per 3-week course at the recommended dose, assuming a body weight of 70 kg, and does not include wastage.

5.2 Summary of Cost Comparison

According to a clinical expert consulted by CADTH, some treatment centres are capable of using sterile conditions to extend the beyond use date of Avastin®, allowing for vial sharing between patients, and thus minimizing wastage. As MVASI™ appears to be packaged in a similar manner and reports an identical list of non-medicinal ingredients to those of Avastin®,[1,2] it is assumed that facilities that are already practicing vial sharing of bevacizumab will continue to do so with MVASI™. In centres that lack the facilities, or that have insufficient patient volume to make such vial sharing efficient, additional savings would be seen with the use of MVASI™ as a larger volume of product (infused and discarded) would be replaced by the less expensive biosimilar.

For the treatment of mCRC, at the submitted price, the use of MVASI™ is associated with a savings of $466 per 70 kg patient per 14-day treatment cycle when compared with the wholesale price of the reference product, Avastin®,[3] if no wastage of excess medication in vials is assumed (see Table 5). Should unused medication in vials need to be discarded, each 70 kg patient would

require 400 mg of product (350 mg infused, 50 mg discarded), leading to a savings of $533 when MVASI™ is used in place of the reference product.

Bevacizumab is not currently reimbursed by provincial drug plans for the treatment of NSCLC, (see Section 7). Should this change in the future, at the submitted price, the use of MVASI™ in place of the reference product, Avastin®, (based on wholesale price)[3] would be associated with a savings of $1,399 per 70 kg patient per 21-day treatment cycle, assuming no wastage of excess medication (see Table 6). Where vial sharing is not possible, each 70 kg patient would require 1,100 mg of product (1,050 mg infused, 50 mg discarded), leading to a savings of $1,466 when MVASI™ is used in place of the reference product.

CADTH also explored the potential savings associated with the use of MVASI™ at the submitted price for patients weighing 50 kg and 90 kg, assuming the wholesale list price of Avastin®[3] and that no wastage occurs (see Table 7).

Table 7: Cost Comparison of MVASI™ and Avastin® for Alternate Patient Weights, Assuming No Wastage

Drug / Comparator	Strength	Price ($)	Recommended Dose	Average Drug Cost (50 kg patient)[a]	Average Drug Cost (90 kg patient)[a]
Metastatic Colorectal Cancer					
MVASI™	25 mg/mL	$385.94 per 100 mg vial; $1,543.77 per 400 mg vial	5mg/kg of body weight once every 14 days	$964.85	$1,736.73
Avastin®	25 mg/mL	$519.17 per 100 mg vial; $2,076.71 per 400 mg vial	5mg/kg of body weight once every 14 days	$1,297.92	$2,336.26
			Incremental savings with MVASI™	**$333.08**	**$599.53**
Non-Small Cell Lung Cancer					
MVASI™	25 mg/mL	$385.94 per 100 mg vial; $1,543.77 per 400 mg vial	15mg/kg of body weight once every 3 weeks	$2,894.55	$5,210.19
Avastin®	25 mg/mL	$519.17 per 100 mg vial; $2,076.71 per 400 mg vial	15mg/kg of body weight once every 3 weeks	$3,893.78	$7,008.80
			Incremental savings with MVASI™	**$999.23**	**$1,798.61**

[a] Cost per administration every 14 days (mCRC) or three weeks (NSCLC).

Additional Issues for Consideration

This price comparison is based on the wholesale list price of the reference product, Avastin®, as retrieved from the IQVIA Delta PA database.[3] Actual costs reimbursed by Canadian public plans for Avastin® are unknown; thus, the true extent of savings or incremental costs associated with the submitted-price MVASI™ are unknown.

Section 6: Implementation Considerations

6.1 Patient and Provider Support Programs

Will a patient support program be made available by the manufacturer? ☒ Yes or ☐ No
Will a health care provider support program be made available by the manufacturer? ☒ Yes or ☐ No

6.2 Summary of Patient Input

This section is intended to be a summary of the patient input based on the perspectives of patient groups providing input on this biosimilar submission. The original patient input submission(s) are shared with the pan-Canadian Pharmaceutical Alliance (pCPA) and participating drug plans and cancer agencies and are published on CADTH's website.

Three patient organizations, Colorectal Cancer Canada (CCC), Ontario Lung Association (OLA), and Colorectal and Lung Cancer Canada (LCC), provided input for bevacizumab for colorectal cancer and non-small cell lung cancer (NSCLC). Some participants surveyed by CCC had some familiarity with biosimilars. Using survey data, CCC identified 20% of patients (N = 6) as "very familiar," 66.7% (N = 20) as "somewhat familiar," and 13.3% (N = 4) as "not at all familiar." Information about biosimilars was obtained by participants through a number of sources, including health care providers (5%, N = 1), patient group organization (87%, N = 29), and websites (9%, N = 3). As a result of the educational session delivered by CCC, 67% of respondents were aware of a biosimilar that would treat their type of cancer. Information was provided from the OLA using a health support group (N = 6) and from previous submissions to CADTH over the past three years. The OLA did not ask respondents about their familiarity with biosimilars or awareness of biosimilars for their condition.

For participants surveyed by CCC who were using a biologic (N = 19), one patient had discussed with their treating physician the possibility of switching from a biologic therapy to a biosimilar. When survey participants were asked to consider how important three factors would be in their decision to start treatment with a biosimilar rather than the reference biologic, 37% of survey respondents believed head-to-head clinical trials showing no significant differences in efficacy and safety is important; 31% believed evidence from post-approval long-term monitoring of effectiveness is important; and 58% maintained biosimilar-induced side effects should be captured. Cost was an additional important factor identified by respondents. CCC stated that, based on the survey results, it was quite evident further patient education was required to properly inform patients and caregivers on the biosimilar drugs. OLA did not ask respondents if they discussed switching to a biosimilar with their doctor, and while they did not ask survey participants specifically about the previously identified factors, they did determine that patients desired fewer medical appointments, decreased cost, and a therapy that would give them more energy and less dependence on caregivers.

None of the participants surveyed by the CCC had experience with MVASI™. When participants were asked about their expectations for side effects, 83.33% of respondents said they would expect to experience similar side effects to those observed with the reference biologic (Avastin®); 10% would expect to experience fewer side effects than those observed with Avastin®; and 6.66% would expect to experience none. Two-thirds of respondents would expect no variability in side effects or benefits between the reference biologic and MVASI™ if they were switched from the reference biologic (Avastin®) to MVASI™. CCC noted that participants found the marginal variability of biosimilarity to be disconcerting and that it resulted in a number of additional questions that could not be properly explored within the confines of the educational session. They suggested that a level of skepticism and anxiety among patients and their families may be the default response when asked to consider treatment with a biosimilar, unless they are properly informed. Patients with metastatic disease did strongly express the following: decisions about prescribing biosimilars should be made between the treating oncologist and their patient on the grounds of clinical efficacy and not solely on price reductions. The OLA did not ask respondents about MVASI™ or their use of biosimilars specifically.

Four (14.3%) participants surveyed by the CCC had accessed a pharmaceutical patient assistance/support program for the reference biologic and described the following as benefits of the program: "It was reassuring to have someone else discuss your treatment and symptoms"; "Info abut side effects to watch for such as bleeding, hypertension"; "Pamphlet and side effects." During the educational session, most patients were surprised to learn that such programs exist and were curious as to why they had

never been made aware of these programs upon being prescribed the reference biologic. They felt they could have benefited from accessing such a program. A large majority of respondents (82.75%) would wish to see a pharmaceutical patient assistance/support program provided for patients accessing the biosimilar under review. The OLA did not ask respondents about accessibility considerations. Reoccurring themes identified in the CCC feedback included the desire for introducing MVASI™ in multiple lines of therapy for the metastatic population and the potential cost savings and accessibility implications of MVASI™.

LCC stated that it is difficult for them to provide comments given that bevacizumab is not a standard of care for patients with unresectable advanced, metastatic, or recurrent non-squamous non-small cell lung cancer and it is also not publicly covered in Canada. LCC did state that it believes patients should not be forced to switch to a biosimilar but rather the decision should be made following a discussion between the patient and their physician.

Please see Appendix A for the full input from patient groups.

6.3 Summary of Clinician Input

This section is intended to be a summary of the clinician input based on the perspectives of registered clinicians providing input on this biosimilar submission. The original clinician input submission(s) are shared with the pan-Canadian Pharmaceutical Alliance (pCPA) and participating drug plans and cancer agencies and are published on CADTH's website.

One clinician group and one individual clinician provided input for bevacizumab for colorectal cancer and non-small cell lung cancer (NSCLC).

With regards to awareness about biosimilars, both inputs identified the clinicians as being somewhat familiar with biosimilars and how they are approved in Canada. Clinicians identified education via participation on advisory boards of various companies as a source of information. One clinician input stated that they were unaware of other brands of biosimilars available to treat the requested indication, while the other input stated that awareness of another (unspecified) branded product had been available for years.

When initiating a patient on a biosimilars, one input stated that for MVASI™ for colorectal cancer, they would initiate a patient in the metastatic setting in first-line. Alternatively, the other input stated that they would initiate a patient or switch a patient to a biosimilar as long as there is rigorous evidence suggesting bioequivalence and a transparent approval process. These clinicians indicated they would use MVASI™ the same way as bevacizumab in both the adjuvant and metastatic setting. However, they were unsure if there was demonstrated bioequivalence for the indications. The clinicians also stated that the decision to use a biosimilar is often not up to the clinician and may be made by the hospital. In regards to switching a patient to a biosimilar from the reference biologic drug, one clinician input stated that they supported switching once the biosimilars became available.

When asked to consider the knowledge that biosimilars are considered to be effective and safe by the regulatory body and using a biosimilar could help to increase access by other patients to new therapies, both clinician groups stated that the information was important to consider for their prescribing decision. Clinicians recognized that the reduced cost to the health care system as a benefit to biosimilars.

Both clinician inputs stated that they were unaware of patient support programs specific to the biosimilar under review. One clinician group indicated that lack of evidence and differences in pre-medication may be potential barriers to prescribing a biosimilar.

Both inputs said that the clinicians would use the biosimilar bevacizumab (MVASI™) for indications approved by Health Canada that have not been reviewed by the pan-Canadian Oncology Drug Review in clinical practice based on evidence of bioequivalence and input from all relevant disease site groups.

Please see Appendix B for the full input from clinicians.

6.4 Summary of Jurisdictional Input

6.4.1 Summary

Jurisdictional input on biosimilars is provided by the pan-Canadian Oncology Drug Review (pCODR) Provincial Advisory Group (PAG), which includes representatives from each of the participating provincial and territorial Ministries of Health, as well as provincial cancer agencies. PAG provides advice to CADTH on pharmaceutical issues and identifies operational and implementation considerations for drugs being reviewed through the pCODR process. The input provided in this summary is intended to help inform product negotiations by the pan-Canadian Pharmaceutical Alliance (pCPA).

From the perspective of the participating provincial and territorial Ministries of Health and provincial cancer agencies, biosimilars have the potential to provide long-term cost reductions, which can be reinvested to help ensure the sustainability of drug funding and provide reimbursement for new drugs where there is currently an unmet therapeutic need. The following are some of the common considerations that are taken into account when pCPA and the participating provincial and territorial Ministries of Health and provincial cancer agencies determine whether or not a biosimilar should be reimbursed and the appropriate conditions for reimbursement:

Approved indications	• Potential differences in the Health Canada–approved indications that have been issued for the biosimilar under review compared with the reference product or other biosimilar products. • Potential for the biosimilar to be used for indications that have been approved for the reference product but have not been approved by Health Canada.
Treatment initiation	• Patient perspectives regarding the biosimilar under review (as specified in the patient group input provided to CADTH). • Identification of the patient population for whom treatment with the biosimilar under review would be most appropriate. • Setting where treatment with the drug is likely to be initiated (e.g., community versus hospital setting).
Reimbursement status	• Current reimbursement status of the reference product and/other biosimilar products across the participating drug plans.
Cost savings	• Magnitude of cost savings offered by the biosimilar under review relative to the reference product and/or other biosimilar products. • Potential for dose escalation of the biosimilar under review.
Patient support programs	• Availability of a patient support program for the biosimilar under review. • Characteristics of any patient support programs for the biosimilar under review relative to those offered for the reference product and/or other biosimilar products.
Switching to the biosimilar	• Evidence regarding the safety and effectiveness of switching a patient from the reference product or another biosimilar to the biosimilar under review. • Patient perspectives regarding switching from the reference product and/or other biosimilar products to the biosimilar under review. • Jurisdictional policies regarding switching from the reference product or another biosimilar to the biosimilar under review.

6.4.2 Switching Evidence

CADTH conducted a Rapid Response in which no relevant literature was found regarding the clinical effectiveness of switching from Avastin® or other biosimilars to MVASI™ for patients with metastatic colorectal cancer or locally advanced, metastatic, or recurrent non-small cell lung cancer.[4]

Section 7: Public Drug Program Funding Status for Reference Product and Other Funded Biosimilars

For each indication that is approved by Health Canada for the biosimilar (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 and other funded biosimilars, if applicable. CADTH may update the information provided by the manufacturer with new information provided by the participating jurisdictions, as required.

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
–	Information not available

Listing Status for Avastin® for Indications Approved by Health Canada for MVASI™

Indication(s)	pCODR Participating Drug Plans													
	BC	**AB**	**SK**	**MB**	**ON**	**NB**	**NS**	**PE**	**NL**	**YK**	**NT**	**NIHB**	**DND**	**VAC**
For first-line treatment of patients with **metastatic carcinoma of the colon or rectum in combination with fluoropyrimidine based chemotherapy (mCRC)**	RES	RES	RES	RES	RES	RES	RES	RES	-	-	-	-	-	-
For treatment of patients with **unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer** in combination with carboplatin/paclitaxel chemotherapy regimen (NSCLC)	NB	NB	NB	NB	NB	NB	NB	NB	NB	-	-	NB	-	-

AB = Alberta; BC = British Columbia; DND = Department of National Defence; MB = Manitoba; NB = New Brunswick; 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.

Listing Status for Avastin® for Other Uses Reviewed by CADTH — NOT HEALTH CANADA APPROVED INDICATIONS FOR AVASTIN® OR MVASI™

Indication(s)	pCODR Participating Drug Plans													
	BC	AB	SK	MB	ON	NB	NS	PE	NL	YK	NT	NIHB	DND	VAC
Request for Funding: In combination with **capecitabine, for the first-line treatment of advanced or metastatic colorectal cancer (CRC)** for patients who are not suitable for oxaliplatin or irinotecan-based therapy	UR according to CADTH website* *it appears it may be covered, see criteria below	UR	RES	RES	RES	RES	UR	UR	UR	-	-	NB	-	-
Request for Funding: In combination with chemotherapy for the treatment of patients with **persistent, recurrent, or metastatic carcinoma of the cervix** **NOT AN APPROVED INDICATION BY HEALTH CANADA**	RES	RES	RES	RES	RES	RES	RES	UR	RES	-	-	-	-	-

AB = Alberta; BC = British Columbia; DND = Department of National Defence; MB = Manitoba; NB = New Brunswick; 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.

Listing Status for Avastin® for Other Uses Reimbursed by Provinces — NOT HEALTH CANADA APPROVED INDICATIONS FOR AVASTIN OR FOR MVASI™

Indication(s)	pCODR Participating Drug Plans													
	BC	AB	SK	MB	ON	NB	NS	PE	NL	YK	NT	NIHB	DND	VAC
For treatment in 2nd or 3rd line in mCRC in patients who have not previously received Avastin	RES	RES	RES	-	NB	-	-	RES	-	-	-	NB	-	-
Small bowel cancer or appendiceal adenocarcinomas	-	-	-	-	RES	-	-	RES	-	-	-	NB	-	-

AB = Alberta; BC = British Columbia; DND = Department of National Defence; MB = Manitoba; NB = New Brunswick; 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 public drug program/cancer agency. Use a separate table for each indication and add or delete rows as necessary.

Restricted Benefit Criteria for Avastin® for the Treatment of mCRC in Combination With Fluoropyrimidine Based Chemotherapy

Drug Program/ Cancer Agency	Criteria for Restricted Benefit
BC	**Palliative Combination Chemotherapy for Metastatic Colorectal Cancer Using Irinotecan, Bevacizumab and Capecitabine (GICIRB)** ELIGIBILITY: • First line therapy for locally advanced, locally recurrent or metastatic colorectal adenocarcinoma, not curable with surgery or radiation not suitable for GIFFIRB. • Consideration of first line oxaliplatin-based therapy (GICOXB) should be given for those patients who have Gilbert's Syndrome or who may be compromised by potential irinotecan toxicities • Second line therapy will be considered only for those patients who have undergone resection of metastasis and therefore were not suitable for first-line therapy with bevacizumab • No major surgery within 28 days of administration of therapy • No untreated CNS metastases • ECOG performance status less than or equal to 2 • Adequate marrow reserve (ANC greater than or equal to 1.5 x 10^9/L, platelets greater than 100 x 10^9/L) • Adequate renal (Creatinine less than or equal to 1.5 x ULN) and liver function (bilirubin less than or equal to 35 micromol/L; ALT/ Alkaline Phosphatase less than or equal to 5 x ULN) • Caution in patients with: 1) previous pelvic radiotherapy; 2) recent MI; 3) uncontrolled angina, hypertension, cardiac arrhythmias, congestive heart failure, 4) renal disease including proteinuria, 5) bleeding disorders, 6) previous anthracycline exposure, 7) prior radiation to the chest wall or other serious medical illness • Caution in patients with baseline greater than 3 loose BM per day (in patients without colostomy or ileostomy) • Caution in patients with recent (less than 6 months) arterial thromboembolic events EXCLUSIONS: • Suitable candidate for infusional Fluorouracil protocol (GIFFIRB) • Severe renal impairment (Creatinine Clearance less than 30 mL/min) • Suspected dihydropyrimidine dehydrogenase (DPD) deficiency (see Precautions) **Palliative Combination Chemotherapy for Metastatic Colorectal Cancer Using Oxaliplatin, Bevacizumab and Capecitabine (GICOXB)** • First line therapy for locally advanced, locally recurrent or metastatic colorectal adenocarcinoma, not curable with surgery or radiation • Second line therapy will be considered only for those patients who have undergone resection of metastasis and therefore were not suitable for first-line therapy with bevacizumab

Drug Program/ Cancer Agency	Criteria for Restricted Benefit
	• No major surgery within 28 days of administration of therapy • No untreated CNS metastases • ECOG performance status less than or equal to 2 • Adequate marrow reserve • Adequate renal and liver function • Caution in patients with: 1) previous pelvic radiotherapy; 2) recent MI; 3) uncontrolled angina, hypertension, cardiac arrhythmias, congestive heart failure, renal disease including proteinuria, bleeding disorders, previous anthracycline exposure, prior radiation to the chest wall or other serious medical illness • Caution in patients with recent (less than 6 months) arterial thromboembolic events EXCLUSIONS: • Suitable candidate for infusional fluorouracil protocol (GIFFOXB) • Severe renal impairment (Creatinine Clearance less than 30 mL/min) • Suspected dihydropyrimidine dehydrogenase (DPD) deficiency (see Precautions) • Severe pre-existing peripheral neuropathy • Avoid in patients with congenital long QT syndrome **Palliative Combination Chemotherapy for Metastatic Colorectal Cancer Using Irinotecan, Fluorouracil, Leucovorin and Bevacizumab (GIFFIRB)** • First line therapy for locally advanced, locally recurrent or metastatic colorectal adenocarcinoma, not curable with surgery or radiation, and for adenocarcinoma of the appendix and small bowel. • Consideration of first line oxaliplatin-based therapy (UGIFFOXB) should be given for those patients who have Gilbert's Syndrome or who may be compromised by potential irinotecan toxicities • Second line therapy will be considered only for those patients who have undergone resection of metastasis and therefore were not suitable for first-line therapy with bevacizumab • No major surgery within 28 days of administration of therapy • No untreated CNS metastases • ECOG performance status less than or equal to 2 • Adequate marrow reserve (ANC greater than or equal to 1.5 x 10^9/L, platelets greater than or equal to 100 x 10^9/L) • Adequate renal (Creatinine less than or equal to 1.5 x ULN) and liver function (bilirubin less than or equal to 35 micromol/L; ALT and Alkaline Phosphatase less than or equal to 5 x ULN) • Caution in patients with: 1) previous pelvic radiotherapy; 2) recent MI; 3) uncontrolled angina, hypertension, cardiac arrhythmias, congestive heart failure, renal disease including proteinuria, bleeding disorders, previous anthracycline exposure, prior radiation to the chest wall or other serious medical illness • Caution in patients with baseline greater than 3 loose BM per day (in patients without colostomy or ileostomy) • Caution in patients with recent (less than 6 months) arterial thromboembolic events

Drug Program/ Cancer Agency	Criteria for Restricted Benefit
	EXCLUSIONS: • Suspected dihydropyrimidine dehydrogenase (DPD) deficiency (see Precautions) **Palliative Combination Chemotherapy for Metastatic Colorectal Cancer Using Oxaliplatin, Fluorouracil, Leucovorin and Bevacizumab (GIFFOXB)** • First line therapy for locally advanced, locally recurrent or metastatic colorectal adenocarcinoma, not curable with surgery or radiation, and for adenocarcinoma of the appendix and small bowel. • Second line therapy will be considered only for those patients who have undergone resection of metastasis and therefore were not suitable for pre-operative therapy with bevacizumab • No major surgery within 28 days of administration of therapy • No untreated CNS metastases • ECOG performance status less than or equal to 2 • Adequate marrow reserve (ANC greater than or equal to 1.2 x 10^9/L, platelets greater than or equal to 100 x 10^9/L) • Adequate renal (Creatinine less than or equal to 1.5 x ULN) and liver function (bilirubin less than or equal to 26 micromol/L; ALT/ Alkaline Phosphatase less than or equal to 5 x ULN) • Caution in patients with: 1) previous pelvic radiotherapy; 2) recent MI; 3) uncontrolled angina, hypertension, cardiac arrhythmias, congestive heart failure, renal disease including proteinuria, bleeding disorders, previous anthracycline exposure, prior radiation to the chest wall or other serious medical illness • Caution in patients with baseline greater than 3 loose BM per day (in patients without colostomy or ileostomy) • Caution in patients with symptomatic peripheral neuropathy • Caution in patients with recent (less than 6 months) arterial thromboembolic events EXCLUSIONS: • Suspected dihydropyrimidine dehydrogenase (DPD) deficiency (see Precautions) • Avoid oxaliplatin in patients with congenital long QT syndrome. Reference for all protocols: http://www.bccancer.bc.ca/health-professionals/clinical-resources/chemotherapy-protocols/gastrointestinal
AB	• In combination with chemotherapy with one line of chemotherapy for the treatment of advanced colorectal cancer (indicated for any line of therapy provided bevacizumab naïve) • Prescribing limited to written authorization by named physicians As recommended by the gastrointestinal tumour program or outlined under group 2 drugs on first page Reference: https://www.albertahealthservices.ca/assets/programs/ps-1025651-drug-benefit-list.pdf
SK	Colorectal Cancer – Metastatic (Unresectable Stage IV) • First line treatment in combination with Irinotecan or Oxaliplatin-based chemotherapy (e.g., FOLFIRI, CAPIRI, FOLFOX, CAPOX) • In combination with chemotherapy (e.g., FOLFIRI or FOLFOX) for borderline resectable disease and conversion therapy

Drug Program/ Cancer Agency	Criteria for Restricted Benefit
	• In combination with a fluoropyrimidine (Capecitabine or Fluorouracil/Leucovorin) for the first-line treatment of patients with advanced or metastatic colorectal cancer for whom combination chemotherapy with Oxaliplatin or Irinotecan is unsuitable, and who have an ECOG performance status of <=2 Reference: http://www.saskcancer.ca/Formulary%2004-13-2018
MB	Colorectal Cancer Gastro-intestinal Regimen Reference Orders (GAST): bevacizumab + de Gramont; bevacizumab + capecitabine; bevacizumab + FOLFOXIRI and; bevacizumab + FOLFIRI Reference: https://www.cancercare.mb.ca/For-Health-Professionals/treatment-guidelines-regimen-reference-orders The treatment protocols refer to the Cancer Care Manitoba (CCMB) Formulary for criteria for use (Note: CCMB Formulary not available online).
ON	Funded for use in treatment regimens: CAPE+BEVA: capecitabine + bevacizumab; FOLFIRI+BEVA: folinic acid (leucovorin)-fluorouracil-irinotecan-bevacizumab; MFOLFOX6+BEVA; folinic acid (leucovorin)-fluorouracil-oxaliplatin-bevacizumab XELOX+BEVA: capecitabine (Xeloda®)-oxaliplatin-bevacizumab FOLFOXIRI+BEVA: folinic acid (leucovorin)-fluorouracil-oxaliplatin-irinotecan-bevacizumab (Bevacizumab is unfunded in this regimen); FULCVR(W)+BEVA: fluorouracil (weekly)-leucovorin-bevacizumab (Bevacizumab is unfunded in this regimen) Reference: https://www.cancercareontario.ca/en/drugformulary/regimens
NB	Criteria not known. http://www2.gnb.ca/content/gnb/en/departments/health/NewBrunswickCancerNetwork.html
NS	Criteria not known. http://www.cdha.nshealth.ca/nova-scotia-cancer-care-program-3
PEI	Colorectal Cancer metastatic, in one line of therapy and may repeat in patients who did not progress while receiving bevacizumab Also, with oxaliplatin it can be used as a first line treatment in combination with fluoropyrimidine (FOLFOX or CAPOX) only where there is an intolerance or contraindication to irinotecan based therapy. • First line neoadjuvant therapy in combination with fluoropyrimidine (FOLFOX or CAPOX) to downsize potentially resectable metastatic lesions. Bevacizumab may be added to Oxaliplatin based therapy in the neoadjuvant setting. Small bowel cancer can be treated the same as colon cancer. Reference: https://www.princeedwardisland.ca/sites/default/files/publications/oncologyformulary.pdf
NFLD	Metastatic colorectal carcinoma protocols with: a. Irinotecan - Capecitabine (CAPIRI); b. CAPOX + Bevacizumab Regimen: oxaliplatin-capecitabine-bevacizumab (Part I); c. FOLFIRI Regimen + Bevacizumab: irinotecan-fluorouracil-leucovorin-bevacizumab (Part I); d. FOLFOX 85 Regimen + Bevacizumab: oxaliplatin-fluorouracil-leucovorin-bevacizumab (Part I); Protocols: http://www.easternhealth.ca/WebInWeb.aspx?d=2&id=2367&p=1485

Drug Program/ Cancer Agency	Criteria for Restricted Benefit
All others	Unknown

Restricted Benefit Criteria for Avastin® for the Treatment of mCRC in Combination With Capecitabine

Drug Program/ Cancer Agency	Criteria for Restricted Benefit
BC	**Palliative Combination Chemotherapy for Metastatic Colorectal Cancer Using Irinotecan, Bevacizumab and Capecitabine (GICIRB)** ELIGIBILITY: • First line therapy for locally advanced, locally recurrent or metastatic colorectal adenocarcinoma, not curable with surgery or radiation not suitable for GIFFIRB. • Consideration of first line oxaliplatin-based therapy (GICOXB) should be given for those patients who have Gilbert's Syndrome or who may be compromised by potential irinotecan toxicities • Second line therapy will be considered only for those patients who have undergone resection of metastasis and therefore were not suitable for first-line therapy with bevacizumab • No major surgery within 28 days of administration of therapy • No untreated CNS metastases • ECOG performance status less than or equal to 2 • Adequate marrow reserve (ANC greater than or equal to 1.5 x 10^9/L, platelets greater than 100 x 10^9/L) • Adequate renal (Creatinine less than or equal to 1.5 x ULN) and liver function (bilirubin less than or equal to 35 micromol/L; ALT/ Alkaline Phosphatase less than or equal to 5 x ULN) • Caution in patients with: 1) previous pelvic radiotherapy; 2) recent MI; 3) uncontrolled angina, hypertension, cardiac arrhythmias, congestive heart failure, 4) renal disease including proteinuria, 5) bleeding disorders, 6) previous anthracycline exposure, 7) prior radiation to the chest wall or other serious medical illness • Caution in patients with baseline greater than 3 loose BM per day (in patients without colostomy or ileostomy) • Caution in patients with recent (less than 6 months) arterial thromboembolic events EXCLUSIONS: • Suitable candidate for infusional Fluorouracil protocol (GIFFIRB) • Severe renal impairment (Creatinine Clearance less than 30 mL/min) • Suspected dihydropyrimidine dehydrogenase (DPD) deficiency (see Precautions)
SK	In combination with a fluoropyrimidine (Capecitabine or luorouracil/Leucovorin) for the first-line treatment of patients with advanced or metastatic colorectal cancer for whom combination chemotherapy with Oxaliplatin or Irinotecan is unsuitable, and who have an ECOG performance status of <2

Drug Program/ Cancer Agency	Criteria for Restricted Benefit
	Reference: http://www.saskcancer.ca/Formulary%2004-13-2018
MB	Bevacizumab in combination with capecitabine or 5-fluororuracil/leucovorin (de Gramont regimen) for the first line treatment of patients with advanced or metastatic colorectal cancer for whom combination chemotherapy with oxaliplatin or irinotecan is unsuitable and patient has ECOG performance status of 2 or less Reference: https://www.cadth.ca/sites/default/files/pcodr/pcodr_provfund_avastin-capecitabine_mcrc.pdf
ON	Bevacizumab is used in combination with a fluoropyrimidine (capecitabine) for the first-line treatment of patients with metastatic colorectal, small bowel, or appendiceal cancer for whom combination chemotherapy with oxaliplatin or irinotecan is unsuitable. Patients should have ECOG performance status ≤2. (Protocol CAPE+BEV) Reference: https://www.cancercareontario.ca/en/drugformulary/regimens
NB	In combination with a fluoropyrimidine, for the first line treatment of patients with advanced or metastatic colorectal cancer for whom combination chemotherapy with oxaliplatin or irinotecan is unsuitable. Reference: https://www.cadth.ca/sites/default/files/pcodr/pcodr_provfund_avastin-capecitabine_mcrc.pdf

Restricted Benefit Criteria for Avastin® for the Treatment of Cervical Cancer

Drug Program/ Cancer Agency	Criteria for Restricted Benefit
BC	Primary Treatment of Metastatic or Recurrent Cancer of the Cervix with Bevacizumab, CARBOplatin and PACLitaxel (GOCXCATB) • Non-small cell cancer of the cervix (squamous, adenocarcinoma, adenosquamous) • Recurrent or IVb at diagnosis Reference: http://www.bccancer.bc.ca/health-professionals/clinical-resources/chemotherapy-protocols/gynecology
AB	In combination with chemotherapy: • For patients with metastatic (Stage IVB), persistent or recurrent carcinoma of the cervix of all histologic subtypes (except small cell) with good performance status. • For retreatment of patients after a complete response with chemotherapy and bevacizumab and who have been off systemic therapy for a period of 6 months. • Not to be used after progression occurring while on bevacizumab Reference: https://www.albertahealthservices.ca/assets/programs/ps-1025651-drug-benefit-list.pdf

Drug Program/ Cancer Agency	Criteria for Restricted Benefit
SK	Carcinoma of the Cervix • Completion of the SCA Treatment Evaluation Program (STEP) request form for each patient is required for treatment approval • In combination with platinum and Paclitaxel for the treatment of patients with metastatic (Stage IVb), persistent, or recurrent carcinoma of the cervix of all histologic subtypes, except small cell, and who have an ECOG performance status of 0 or 1. Bevacizumab is approved at a dose of 15 mg/kg for treatment until disease progression, unacceptable toxicity or complete response. Reference: http://www.saskcancer.ca/Formulary%2004-13-2018
MB	For the treatment of patients with: • Metastatic, persistent or recurrent cervical carcinoma AND • An Eastern Cooperative Oncology Group performance status of 0 or 1 AND • Adequate renal, hepatic and bone marrow function. Reference: https://www.cadth.ca/sites/default/files/pcodr/pcodr_provfund_avastin-cc.pdf
ON	In combination with chemotherapy for the treatment of patients with metastatic (Stage IVB), persistent, or recurrent carcinoma of the cervix of all histologic subtypes (except small cell); AND • Patient has ECOG ≤ 1 Dosing Regimen: 15mg/kg of body weight given once every 3 weeks as an intravenous infusion Notes: • On a time limited basis (6 months), o Patients who initiated first line chemotherapy prior to January 11, 2016 and whose disease has not progressed will have the option of adding bevacizumab. Patients who have achieved a clinically meaningful response on a first line chemotherapy regimen will have the option of adding bevacizumab when continuation of the same first line regimen is considered clinically appropriate • To be eligible for funding, patients must be able to start bevacizumab in combination with chemotherapy. • Funding will continue until disease progression. Reference: https://www.cadth.ca/sites/default/files/pcodr/pcodr_provfund_avastin-cc.pdf
NB	In combination with platinum and paclitaxel chemotherapy for the treatment of patients with metastatic (stage IVB), persistent, or recurrent carcinoma of the cervix of all histologic subtypes (except small cell) and an ECOG performance status of 0 to 1. Retreatment with bevacizumab plus platinum and paclitaxel may be offered to patients following a complete response and a treatment-free period of at least 6 months. The funded dose is bevacizumab 15 mg/kg intravenously every 3 weeks until disease progression, unacceptable toxicity, or complete response, whichever occurs first Reference: https://www.cadth.ca/sites/default/files/pcodr/pcodr_provfund_avastin-cc.pdf
NS	In combination with chemotherapy for patients with metastatic (stage IVB), persistent or recurrent carcinoma of the cervix of all histologic subtypes (except small cell) and good performance status. Retreatment with bevacizumab plus chemotherapy may be offered to patients who have achieved a complete response (with previous bevacizumab and chemotherapy) and off treatment for at least 6 months. Reference: https://www.cadth.ca/sites/default/files/pcodr/pcodr_provfund_avastin-cc.pdf
NFLD	In combination with chemotherapy for the treatment of patients with metastatic (Stage IVB), persistent, or recurrent carcinoma of the cervix of all histologic subtypes (except small cell) with an ECOG performance status ≤ 1 Reference: https://www.cadth.ca/sites/default/files/pcodr/pcodr_provfund_avastin-cc.pdf
All others	Unknown

Restricted Benefit Criteria for Avastin® for the Treatment of mCRC in 2nd or 3rd Line Without Prior Use

Drug Program/ Cancer Agency	Criteria for Restricted Benefit
BC	Bevacizumab is recommended for use in combination with first-line FOLFIRI chemotherapy (FOLFOX may be considered in selected circumstances). It may also be considered for use in combination with second-line doublet chemotherapy for those patients who did not receive it in first-line. Reference: http://www.bccancer.bc.ca/health-professionals/clinical-resources/cancer-management-guidelines/gastrointestinal/colon In all treatment protocols with the following criteria: • Second line therapy will be considered only for those patients who have undergone resection of metastasis and therefore were not suitable for first-line therapy with bevacizumab Reference for all protocols: http://www.bccancer.bc.ca/health-professionals/clinical-resources/chemotherapy-protocols/gastrointestinal
AB	In combination with chemotherapy with one line of chemotherapy for the treatment of advanced colorectal cancer (indicated for any line of therapy provided bevacizumab naïve) Reference: https://www.albertahealthservices.ca/assets/programs/ps-1025651-drug-benefit-list.pdf
SK	Irinotecan: First or second line treatment in combination with fluoropyrimidine (FOLFIRI or CAPIRI); combination with Bevacizumab only approved for first line treatment Note: Folfiri/Capiri +/- Bevacizumab can be used as next line of treatment after failure of single agent Capecitabine Reference: http://www.saskcancer.ca/Formulary%2004-13-2018
PEI	Colorectal Cancer metastatic, in one line of therapy and may repeat in patients who did not progress while receiving bevacizumab Reference: https://www.princeedwardisland.ca/sites/default/files/publications/oncologyformulary.pdf

Restricted Benefit Criteria for Avastin® for the Treatment of Small Bowel and Appendiceal Adenocarcinomas

Drug Program/ Cancer Agency	Criteria for Restricted Benefit
ON	Funded for first-line treatment of metastatic colorectal, small bowel or appendiceal cancer used in treatment regimens: CAPE+BEVA: Bevacizumab is funded in combination with fluoropyrimidine (i.e. capecitabine) for first line treatment of patients with metastatic colorectal, small bowel or appendiceal cancer for whom combination chemotherapy with oxaliplatin or irinotecan is unsuitable. Patients should have ECOG performance status ≤ 2. FOLFIRI+BEVA: First-line treatment of metastatic colorectal, small bowel or appendiceal cancer mFOLFOX6+BEVA: First-line treatment of metastatic colorectal, small bowel or appendiceal cancer XELOX+BEVA: First-line treatment of metastatic colorectal, small bowel or appendiceal cancer Reference: https://www.cancercareontario.ca/en/drugformulary/regimens
PEI	Small bowel cancer can be treated the same as colon cancer. Reference: https://www.princeedwardisland.ca/sites/default/files/publications/oncologyformulary.pdf

Appendix A: CADTH Biosimilars Patient Group(s) Input

Important Note for Patient Group(s):

Biosimilars Patient Input Template for CADTH CDR and pCODR Programs

Name of the Drug and Indication	**MVASI IN COMBINATION WITH CHEMOTHERAPY IN 1ST LINE TREATMENT OF METASTATIC COLORECTAL CANCER ('MCRC')**
Name of the Patient Group	**COLORECTAL CANCER CANADA ('CCC')**

Introduction

Biologic drugs come from living organisms or from their cells and are often made using biotechnology.

They are used to treat diseases and medical conditions including anemia, diabetes, inflammatory bowel disease, psoriasis, rheumatoid arthritis, hormone deficiency, and some forms of cancer.

A biosimilar is a drug demonstrated to be highly similar to a biologic drug (known as the reference biologic drug) that was already authorized for sale by the regulatory body, Health Canada. Biosimilars are approved based on having no clinically meaningful differences compared with the reference biologic drug product in terms of safety, purity, and efficacy. Biosimilars may enter the market after the expiry of reference biologic drug patents and data protection.

To help inform the advice that you provide to CADTH and that will be shared with the pan-Canadian Pharmaceutical Alliance and participating jurisdictions making a funding decision, please consider the following:

A. Awareness About Biosimilars

1. How familiar are you with biosimilars? (Please specify: very familiar, somewhat familiar, not at all familiar.) Please provide aggregate data, if available.

Upon learning of MVASI's lack of uptake in Canada, Colorectal Cancer Canada (CCC) reached out to online colorectal cancer (CRC) chat groups/forums throughout Canada, the U.S. and Europe to determine if CRC patients/caregivers having experience with the therapy under review could be identified for survey completion. None came forward through our outreach efforts. A strategic plan was, therefore, developed to survey a longstanding, well-versed, colorectal cancer patient and caregiver support group in the greater Toronto area (**CCRAN**) on **October 21, 2018** after delivering a one hour educational session on biosimilars by a CCC employee. The aim of the survey was to gauge colorectal cancer patients' and caregivers' **expectations** concerning the biosimilar under review. A copy of the survey results, containing open-ended replies, is attached.

52 members attended the CCRAN monthly support group meeting led by a CCC support group facilitator/employee on October 21, 2018. Patients and caregivers were initially surveyed by a show of hands to determine biosimilar familiarity. One stage IV colorectal cancer patient had familiarity with biosimilars; he had received the information from his treating medical oncologist. Three other patients had prepared for the session by researching biosimilars online a few days prior to October 21, 2018. The educational session was then delivered containing the following content derived from Health Canada's Fact Sheet on Biologics and Biosimilars https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/fact-sheet-biosimilars.html:

- Definition of a chemotherapeutic, biologic, reference biologic, biosimilar, and a generic

- What is: Avastin (Bevacizumab); MVASI?
- Why are oncology biosimilars entering the Canadian Market? (Expiry of biologic patents)
- What is a pharmaceutical patient assistance/support program?

20 patients (15 Stage IV; 5 Stage III) and **10 caregivers** completed the hard copy survey onsite once the educational information had been delivered in respect of biosimilars. The balance of the support group members (Stage I and II) did not feel comfortable completing the hard copy survey for they felt they did not have a proficient level of understanding with the content required to complete the survey. It is important to note that from the 15 Stage IV patients who completed the survey, 11 patients had experience with the reference biologic (Avastin). The four remaining metastatic patients were identified as follows:

- one patient had experience with Panitumumab in first line therapy;
- one patient did not qualify for any biologic therapy due to IBD;
- another patient had received chemotherapy as neoadjuvant therapy in preparation for her liver resection
- and the last patient refused the biologic therapy in combination with chemotherapy for the treatment of her lung nodules.

After the educational information had been delivered and the survey results had been analyzed, 67% of survey respondents felt somewhat familiar with biosimilars and 20% felt they were very familiar with biosimilars (Q5). In 87% of respondents, CCC was cited as the source of the information obtained on biosimilars (Q6).

2. If you are familiar with biosimilars, how was this information obtained (e.g., from health care provider, patient organization, government or not-for-profit organization, industry, general website, other [please specify])? Please provide aggregate data, if available.

Please see reply to Q1 above.

3. To what degree are you aware of any biosimilars that would treat your condition? (Please specify: aware, not aware.) Please provide aggregate data, if available.

As a result of the educational session delivered, 67% of respondents were aware of a biosimilar that would treat their type of cancer (Q7). Appearing below are some of the open-ended replies furnished by patients and caregivers:

- *I have stage IV cancer treated with avastin. I have become aware of biosimilars as a results of the educational session put on by CCC and would like to see it be available in addition to avastin when required."*
- *I have some knowledge of what a biosimilar is. I was made aware at an information session on Oct. 21/18 at CCRAN and have done some research online."*

B. Treatment Options

1. If you are using a biologic, have you discussed with your doctor about being switched to a biosimilar? (Please specify: yes, no.) Please provide aggregate data, if available.

According to the survey results (Q8), **one patient** had discussed with their treating physician the possibility of switching from a biologic therapy to a biosimilar – it was for the treatment of his **Inflammatory Bowel Disease (**disclosed during the group session**)**.

Question 9, however, did hypothetically ask survey participants if they would be prepared to switch from a reference biologic to a biosimilar if asked to do so by their treating oncologist. Almost 87% of respondents answered "Yes".

In a rather similarly phrased question (Q15), 78.6% of survey respondents would not have a difficult time switching from Avastin to MVASI if it was recommended by their treating oncologist and side effects/benefits were similar. The following open ended replies were furnished:

- *"It would depend on whether or not Avastin is working effectively for me. However, if side effects and benefits are similar, then*

yes, especially if govt assisted.
- *As long as approved by Canadian Regulatory Agency.*
- *I would do what my onc said to do.*
- *It would depend on the reasons. If it was for cost reasons, I would have issues. If it was for more effective treatment, I would have no issues."*

2. As a biosimilar is considered to be effective and safe by the regulatory body, how important would each of the following factors be in your decision to start treatment with a biosimilar rather than the reference biologic drug: (1) head-to-head clinical trials showing no significant difference in efficacy and safety, (2) evidence from (post-approval) long-term monitoring of effectiveness, (3) side effects, (4) other (please specify).

Question 10 provided survey participants with the opportunity to consider how important three factors would be in their decision to start treatment with a biosimilar rather than the reference biologic.
- 37% of survey respondents believe head to head clinical trials showing no significant differences in efficacy and safety is important
- 31% believe evidence from post approval long term monitoring of effectiveness is important
- 58% maintain biosimilar-induced side effects should be captured

Survey respondents were then asked to supply other factors deemed important in their decision to start treatment with a biosimilar:
- *"Based on the assumption that the biosimilar has been approved and met the requirements of Health Canada, then no further evidence would be necessary.*
- *I would like to be comfortable with effectiveness of use in conjunction with chemo.*
- *Reduced price for biosimilar.*
- *Cost.*
- *Availability of biosimilar in 2nd line treatment."*
- *"No.*
- *The fact that it has been approved by Health Canada demonstrates efficacy and safety to me.*
- *Any contraindications to my specific case, of course.*
- *Cost, availability."*

Throughout the delivery of the educational content on biosimilars content on October 21st, patients and caregivers were repeatedly inquiring if there was a stringent approval process in place by the regulatory authority in Canada, thereby, ensuring that the biosimilar is of "equal" effectiveness overall to the reference biologic. If so, this could potentially provide mCRC patients with the opportunity to respond with "equivalence" in a treatment-naïve setting or during a requested switch by the treating oncologist.

A fair amount of time was dedicated to ensuring patients and caregivers understood biosimilars are developed with the intention of being as close as possible to the reference biologic, and that biosimilars do go through a rigorous evaluation approval process to show that they are as safe and effective as the reference biologic. Biosimilars will never be an exact copy, however. The regulation process requires a biosimilar have a similar biochemical structure to the reference biologic and to show the same safety and efficacy in clinical trials. Ultimately, any differences that arise from the manufacturing process do not in any way compromise patient outcomes. A biosimilar, however, is not identical to its reference biologic. It was critically important patients and caregivers understood this before completing the survey so that in the absence of patient experience with the biosimilar under review, the survey could assess patients' expectations with the biosimilar under review. Based on the survey results, however, it was quite evident further patient education was required to properly inform patients and caregivers on the biosimilar drugs.

C. About the Biosimilar Under Review

1. For patients who have experience with a biosimilar, how did you access the biosimilar under review (e.g., clinical trials, a special access or support program, private insurance, public drug plans, other)?

Based on the show of hands (pre-survey), no one in attendance on October 21, 2018 had any experience in respect of MVASI.

2. If you were initiated on a biosimilar, please describe if there were any benefits or side effects experienced with the biosimilar.

Question 13 of the survey gauged survey participants' expectations with respect to MVASI's side effects. 83.33% of respondents would expect to experience similar side effects to those observed with the reference biologic (Avastin). 10% would expect to experience fewer side effects than those observed with Avastin and 6.66% would expect to experience none.

Once again, during the educational session, patients and caregivers presented thoughtful questions when it came to the safety and side effects of biosimilars. They required a "yes" or "no" answer to the following question: ***Will biosimilar side effects be the same as the reference biologic***? While the active substance of a biosimilar must be similar, in molecular and biological terms to that of the reference biologic, there will be some marginal variability of biosimilarity. This was disconcerting to patients and caregivers because it resulted in a number of additional questions that could not be properly explored within the confines of the educational session. Stage IV patients and caregivers made it abundantly clear on October 21st that evidence-based information is required to allow them to make informed decisions and thoughtful choices about biosimilar treatment and patient care. The science of biosimilars and their introduction into the Canadian market can be challenging for the cancer patient, in particular, who is already fraught with a highly demanding disease journey and uncertain outcomes. Consequently, a level of skepticism and anxiety among patients and their families may be the default response when asked to consider treatment with a biosimilar, unless they are properly informed. Question 14 of the survey gauged survey participants' expectations with respect to MVASI's benefits. Results were consistent with those of Q13: 86.66% of respondents would expect to experience benefits that are similar to those observed with the reference biologic.

3. If you were switched from the reference biologic drug to a biosimilar, please describe any benefits or side effects experienced with the reference biologic drug compared with the biosimilar.

In Q16, 66.66% of respondents would **expect** no variability in side effects or benefits between the reference biologic and MVASI, if they were switched from the reference biologic (Avastin) to MVASI. Throughout the educational session, our metastatic patients voiced how eager they are to have more options for the treatment of their disease. Those who have been successfully treating their metastatic disease with the reference biologic are not, however, eager to be pressured into switching to a biosimilar without assessing risk against benefit accurately, and they need the decision making tools to be able to discuss the pros and cons with their healthcare team and patient groups. i.e. "*If both are funded and avastin is working, I would not want to change something that is being effective…."(Q15)*

In Q17(a-b), 96.67% of survey respondents would be willing to take MVASI in first line therapy because, unlike the reference biologic, MVASI is funded by the province due to its cost effectiveness profile. Open ended replies included:

- *"Yes, because I am willing to try anything the doctor would recommend to prolong or save my life.*
- *Same or similar outcome."*

One respondent, however, would be prepared to pay out of pocket for the reference biologic if given the choice. Open ended replies included:

- *"Depends on actual cost but I would seriously consider it.*
- *Depends on cost and financial impact on whole family."*

Metastatic patients did strongly express the following: decisions about prescribing biosimilars should be made between the treating oncologist and their patient on the grounds of clinical efficacy and not solely on price reductions. Switching without the consent of the patient, would introduce unacceptable uncertainties into the doctor-patient decision-making process which cancer patients hold sacrosanct. Our patients do not wish to see the availability of lower-priced biosimilars increase pressure on clinicians (by health providers and insurers) to prescribe the newer alternative on the basis of cost alone. Here are some of the open-ended replies furnished by survey respondents (Q15):

- *"Already comfortable with drug avastin which in my case had no side effects and was in hindsight likely helpful so why change in midstream?*
- *It would depend on the reasons. If it was for cost reasons, I would have issues. If it was for more effective treatment, I would have no issues.*
- *I may if I was experiencing good health (with avastin). I would need to know benefit to me to make the switch as to why? Other than cost related."*

D. Accessibility Considerations

1. Do you have access to a support program with the biosimilar? What aspects of the support program do you find to be beneficial?

The survey results highlight the importance of furnishing a pharmaceutical patient assistance/support program for patients, as much as for nonfinancial and financial reasons. For those 4 metastatic patients (14.28%) who accessed a pharmaceutical patient assistance/support program for the reference biologic (Q18), the benefits described by patients in the open-ended replies were as follows:

- *"It was reassuring to have someone else discuss your treatment and symptoms.*
- *Info abut side effects to watch for such as bleeding, hypertension.*
- *Pamphlet and side effects."*

One patient commented on how critically important such a program would have been to them if they would have had the opportunity to access it:

- *"No support provided at PMH only financial as I qualified for funding. I could have benefited greatly from clarification and information!!"*

Pharmaceutical patient assistance/support programs are committed to providing support to patients to optimize access to treatments by navigating through the gaps and barriers that may exist in the Canadian healthcare and reimbursement system. Patients, however, prefer to receive information from their trusted patient groups representatives and/or patient group website/educational materials. During the educational session, most patients were surprised to learn that such programs exist and were curious as to why they had never been made aware of these programs upon being prescribed the reference biologic. They felt they could have benefited from accessing such a program.

In Q20, patients who accessed a patient assistance/support program for the reference biologic specified what components of that program they would wish to see appearing in a similar program for MVASI. These included:

- *Additional Testing.*
- *Side effects, benefits.*
- *Money and access.*

2. If you were previously on a reference biologic drug, does the biosimilar provide a similar support program?

In Q19, 82.75% of respondents would wish to see a pharmaceutical patient assistance/support program provided for patients accessing the biosimilar under review. This survey result merely reinforces the patient and caregiver's need to access a program that focuses on enhancing care for patients who are managing a complex medical condition requiring treatment with high cost specialty drugs, including reimbursement navigation. During the educational session, CCC was reminded by our stage IV patients and their caregivers that patients are constantly seeking the optimal cancer patient experience. This includes:

- a thoughtful dialogue between the patient and treating oncologist/health care team
- access to reliable and accurate information
- accessing their therapy quickly and easily
- provision of supportive care

Any program that can enhance or optimize any of the above noted points would surely be welcome by patients and their caregivers, including a pharmaceutical patient assistance/support program.

E. Additional Comments (Optional)

Question 20 of the survey allowed for additional open-ended replies to be furnished by patients and caregivers. There were some emerging themes that captured the attention of CCC. Appearing below are some of the open-ended replies provided by survey respondents:

- *"Given that biosimilars will increase survivorship, then one should draw only one conclusion and approve MVASI for all lines of treatment for crc.*
- *It is important to make it available through govt funding. Cancer is already financially exhausting as is, it's important that cancer patients not be added with the additional stress of affording or not affording a drug that can be beneficial to their well being.*
- *If it is truly proven to be effective, it needs to be available.*
- *I was not eligible for Avastin in first line due to Crohns. However, Crohns is now gone after ileostomy surgery and I would like to access drug in second line. However, avastin is not covered by Ontario so any competitor to the market could provide coverage for me in 2nd line, or at the very least, at a cheaper cost.*
- *I believe the more options available for stage iv patients, the better. Expecially treatments that extend past first line.*
- *Would like to see a biosimilar in second phase if refused in first phase.*
- *I would like to see this drug be made available for 1st and 2nd line treatment.*
- *I would like to see a biosimilar be made available for 2nd line treatment regardless of what they had as a first line treatment. Eg avastin or nothing! If it makes sense for a patient in 2nd line, it should be available.*
- *It's important for HC to provide cancer pats with support for all alternative drugs.*
- *I would like to see MVASI used for both 1st and 2nd line therapy.*
- *It makes sense to introduce a drug that can be effective and less expensive.*
- *I would like to see MVASI approved for 2nd and 3rd line treatment because currently there is not biologic for RAS mutant patients.*
- *This drug is needed in Ontario. It makes sense as it is HC approved and biosimilar.*
- *We need this support.*
- *Need for options for metastatic population.*
- *Better educated."*

50% of survey respondents focused on introducing MVASI in multiple lines of therapy for the metastatic population ("*I would like to see MVASI be used for both 1st and 2nd line therapy*"). Patients and caregivers are also suggesting that since MVASI can offer a savings in price compared to the reference biologic, it can, theoretically, give more patients additional access. For those patients who did not qualify for the biosimilar in the first line setting, survey respondents are recommending that the biosimilar cost savings could

warrant the funding approval of the biosimilar in the second line setting for the subset of the metastatic population who did not access the therapy in first line but eventually became candidates in second line:

- "*I was not eligible for Avastin in first line due to Crohns. However, Crohns is now gone after ileostomy surgery and I would like to access drug in second line. However, avastin is not covered by Ontario so any competitor to the market could provide coverage for me in 2nd line"*
- *"I would like to see a biosimilar in second phase if refused in first phase".*

A patient also introduced the prospect of funding the biosimilar in 3rd line for the RAS Mutant population

- "*I would like to see MVASI approved for 2nd and 3rd line treatment because currently there is not biologic for RAS mutant patients".*

In conclusion, while the survey results support patient and caregiver funding approval of MVASI, the adoption of MVASI into the Canadian oncology setting requires many considerations to ensure maximal uptake, high quality care, optimal patient outcomes and delivery of the biosimilar under review at a reduced price. This is the first biosimilar under review in the oncology space and as such this is CCC's first biosimilar patient group input submission, which was fraught with a number of challenges. This included the lack of patient and caregiver education, awareness and comfort with the use of a biosimilar for the treatment of MCRC. Most patients and caregivers were not familiar with biosimilars which necessitated the delivery of a biosimilar educational session pre-survey administration. The survey results clearly indicate that this session did not adequately deliver sufficient educational biosimilar content. While the survey did not asses the patient/caregiver experience in respect of the biosimilar under review, it attempted to assess their expectations in respect of same. Patients expressed doubts and concerns about the biosimilar's safety and efficacy but they did wish to be informed and involved in decision-making concerning biosimilars and indicated their need to provide informed consent if receiving therapy with a biosimilar. This is particularly important for the MCRC patient who is concerned for their survival.

Survey respondents were also of the opinion that the cost of the treatment should not come before the effectiveness or safety and tolerance of the therapy. They did also note that, perhaps, a greater number of patients would be treated with biologics due to the lower price of the biosimilar, by creating a competitive environment and by extending it in other lines of therapy ("…..*avastin is not covered by Ontario so any competitor to the market could provide coverage for me in 2nd line, or at the very least, at a cheaper cost")*. Survey respondents would trust their treating physician to make the decision to use the biosimilar in their treatment of MCRC, assuming of course the patient would play a role in that decision making process through the provision of informed consent.

The introduction of oncology biosimilars is new in Canada. A concerted effort is required to educate patients and caregivers on biosimilar products and their appropriate use. Patient groups can offer assistance in this area as thought leaders. The thoughtful development of educational materials addressing the differences between biologics and biosimilars, biosimilar efficacy, safety concerns and side effects is strongly needed for oncology patients and their families. In order to provide long term confidence of biosimilars to our patient population, consideration should be given to the collection of real world data (RWD) post marketing.

We support a positive funding recommendation for MVASI for the first line treatment of metastatic colorectal cancer in combination with chemotherapy. We believe it aligns well with the needs of our metastatic colorectal cancer patient and caregiver population, provided:

- therapeutic educational programs are developed and furnished for patients and caregivers, including pharmaceutical patient assistance/support programs,
- patients are involved in decision-making when starting a biosimilar,
- the cost of the treatment does not come before the effectiveness or safety and tolerance of the therapy
- the decision to switch from a reference biologic to the biosimilar rests entirely between clinician and patient through an exercise of informed choice and informed consent
- consideration be given to the collection of RWD post marketing to provide long term confidence on the use of biosimilar therapy.

CADTH

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH CDR and pCODR programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

   No

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

   No

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company
Abbvie Corp
AMGEN Canada
Astra Zeneca Canada
BioCanRx
Boehringer Ingelheim Ltd
Bristol Myers Squibb Canada
Eli Lilly Canada
Ferring Pharmaceuticals
Hoffman La Roche
Janssen Inc
Merck Canada
Novartis Pharma
Pfizer Canada
Taiho Pharma Canada

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Barry D. Stein
Position: President & CEO
Patient Group: Colorectal Cancer Canada
Date: October 31, 2018

CADTH

Biosimilars Patient Input Template for CADTH CDR and pCODR Programs

Name of the Drug and Indication	**Mvasi (Bevacizumab) / Non-Small Cell Lung Cancer Biosimilar**
Name of the Patient Group	**The Lung Association – Ontario**

Introduction

Biologic drugs come from living organisms or from their cells and are often made using biotechnology.

They are used to treat diseases and medical conditions including anemia, diabetes, inflammatory bowel disease, psoriasis, rheumatoid arthritis, hormone deficiency, and some forms of cancer.

A biosimilar is a drug demonstrated to be highly similar to a biologic drug (known as the reference biologic drug) that was already authorized for sale by the regulatory body, Health Canada. Biosimilars are approved based on having no clinically meaningful differences compared with the reference biologic drug product in terms of safety, purity, and efficacy. Biosimilars may enter the market after the expiry of reference biologic drug patents and data protection.

To help inform the advice that you provide to CADTH and that will be shared with the pan-Canadian Pharmaceutical Alliance and participating jurisdictions making a funding decision, please consider the following:

A. Awareness About Biosimilars

1. How familiar are you with biosimilars? (Please specify: very familiar, somewhat familiar, not at all familiar.) Please provide aggregate data, if available.

This question was not asked of the respondents, so we are not able to answer it accurately.

2. If you are familiar with biosimilars, how was this information obtained (e.g., from health care provider, patient organization, government or not-for-profit organization, industry, general website, other [please specify])? Please provide aggregate data, if available.

The information provided from the Ontario Lung Association in this submission was obtained from feedback received from a Toronto based lung health support group, comprised of six members (one with lung cancer, one with IPF, and four with COPD), as well as one phone interview with a patient living with lung cancer. Both of these were completed during the month of September 2018. In addition, The Lung Association – Ontario has obtained feedback for previous submissions to CADTH over the past three years and that data was referenced for this submission. All data gathered was from people residing in Canada. Input from a certified respiratory educator was also used to complete this submission.

3. To what degree are you aware of any biosimilars that would treat your condition? (Please specify: aware, not aware.) Please provide aggregate data, if available.

This question was not asked of the respondents, so we are not able to answer it accurately.

B. Treatment Options

1. If you are using a biologic, have you discussed with your doctor about being switched to a biosimilar? (Please specify: yes, no.) Please provide aggregate data, if available.

This question was not asked of the respondents, so we are not able to answer it accurately.

2. As a biosimilar is considered to be effective and safe by the regulatory body, how important would each of the following factors be in your decision to start treatment with a biosimilar rather than the reference biologic drug: (1) head-to-head clinical trials showing no significant difference in efficacy and safety, (2) evidence from (post-approval) long-term monitoring of effectiveness, (3) side effects, (4) other (please specify).

The desire for fewer medical appointments was mentioned several times, as was a wish for less cost burden. One patient paid, out of her own pocket, for a service to drive her to all treatment appointments and back home again. The secondary costs of this illness and treatments were also mentioned. For example, due to the weight loss and need for good nutrition, the patient was instructed to buy certain foods (such as Ensure) and these foods are quite expensive especially for those seniors who are living on a fixed income / pension.

Overall, patients would like their treatments to provide enough help that they will experience improved independence and require less assistance from others. The desire for more / increased energy was noted many times.

Training for general practitioners (GPs) was also mentioned as a need, as these patients felt their GPs needed to know more about lung diseases so there would not be unnecessary delays in diagnosis and treatment.

None of the interviewees entertained the idea of not being treated, even those with advanced disease. Their questions were focused more so on the issues of understanding the treatment options and what those options actually meant for them. Several stated the need for clear communication about these topics as an important aspect of their decision-making and coping.

It is noteworthy that the caregivers of those living with lung cancer experience many of the same negative impacts on their lives as the patients themselves. They too indicate that caring for them has affected their work, finances, relationships with family and friends, and their physical and leisure activities. As well, their independence and the ability to travel and socialize were impacted. Finally, an overarching theme was the emotional toll of watching those with lung cancer suffer in pain, knowing there is little you can do to alleviate the discomfort and pain.

C. About the Biosimilar Under Review

1. For patients who have experience with a biosimilar, how did you access the biosimilar under review (e.g., clinical trials, a special access or support program, private insurance, public drug plans, other)?

This question was not asked of the respondents, so we are not able to answer it accurately.

2. If you were initiated on a biosimilar, please describe if there were any benefits or side effects experienced with the biosimilar.

This question was not asked of the respondents, so we are not able to answer it accurately.

3. If you were switched from the reference biologic drug to a biosimilar, please describe any benefits or side effects experienced with the reference biologic drug compared with the biosimilar.

This question was not asked of the respondents, so we are not able to answer it accurately.

D. Accessibility Considerations

1. Do you have access to a support program with the biosimilar? What aspects of the support program do you find to be beneficial?

This question was not asked of the respondents, so we are not able to answer it accurately.

2. If you were previously on a reference biologic drug, does the biosimilar provide a similar support program?

This question was not asked of the respondents, so we are not able to answer it accurately.

E. Additional Comments (Optional)

None

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH CDR and pCODR programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

   No – not applicable

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

   No – not applicable

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company
Amgen Canada Inc.

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Peter Glazier
Position: VP Marketing, Development & Public Affairs
Patient Group: The Lung Association - Ontario
Date: November 8th, 2018

CADTH

Biosimilars Patient Input Template for CADTH CDR and pCODR Programs

Name of the Drug and Indication	Bevacizumab (Mvasi) for the treatment of patients with unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer, in combination with carboplatin/paclitaxel chemotherapy regimen
Name of the Patient Group	Lung Cancer Canada

Introduction

Biologic drugs come from living organisms or from their cells and are often made using biotechnology.

They are used to treat diseases and medical conditions including anemia, diabetes, inflammatory bowel disease, psoriasis, rheumatoid arthritis, hormone deficiency, and some forms of cancer.

A biosimilar is a drug demonstrated to be highly similar to a biologic drug (known as the reference biologic drug) that was already authorized for sale by the regulatory body, Health Canada. Biosimilars are approved based on having no clinically meaningful differences compared with the reference biologic drug product in terms of safety, purity, and efficacy. Biosimilars may enter the market after the expiry of reference biologic drug patents and data protection.

To help inform the advice that you provide to CADTH and that will be shared with the pan-Canadian Pharmaceutical Alliance and participating jurisdictions making a funding decision, please consider the following:

A. Awareness About Biosimilars

1. How familiar are you with biosimilars? (Please specify: very familiar, somewhat familiar, not at all familiar.) Please provide aggregate data, if available.

N/A

2. If you are familiar with biosimilars, how was this information obtained (e.g., from health care provider, patient organization, government or not-for-profit organization, industry, general website, other [please specify])? Please provide aggregate data, if available.

N/A

3. To what degree are you aware of any biosimilars that would treat your condition? (Please specify: aware, not aware.) Please provide aggregate data, if available.

N/A

B. Treatment Options

1. If you are using a biologic, have you discussed with your doctor about being switched to a biosimilar? (Please specify: yes, no.) Please provide aggregate data, if available.

N/A

2. As a biosimilar is considered to be effective and safe by the regulatory body, how important would each of the following factors be in your decision to start treatment with a biosimilar rather than the reference biologic drug: (1) head-to-head clinical trials showing no significant difference in efficacy and safety, (2) evidence from (post-approval) long-term monitoring of effectiveness, (3) side effects, (4) other (please specify).

N/A

C. About the Biosimilar Under Review

1. For patients who have experience with a biosimilar, how did you access the biosimilar under review (e.g., clinical trials, a special access or support program, private insurance, public drug plans, other)?

N/A

2. If you were initiated on a biosimilar, please describe if there were any benefits or side effects experienced with the biosimilar.

N/A

3. If you were switched from the reference biologic drug to a biosimilar, please describe any benefits or side effects experienced with the reference biologic drug compared with the biosimilar.

N/A

D. Accessibility Considerations

1. Do you have access to a support program with the biosimilar? What aspects of the support program do you find to be beneficial?

N/A

2. If you were previously on a reference biologic drug, does the biosimilar provide a similar support program?

N/A

E. Additional Comments (Optional)

Bevacizumab is a drug that is rarely used in the treatment of lung cancer in Canada. At this time it is difficult for Lung Cancer Canada to comment given that bevacizumab is not a standard of care for patients with unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer and it is also not publicly covered in Canada.

We do believe patients should not be forced to switch to a biosimilar but rather the decision should be made following a discussion between the patient and their physician.

CADTH

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH CDR and pCODR programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

   N/A

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

   N/A

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Shem Singh
Position: Executive Director
Patient Group: Lung Cancer Canada
Date:2018/10/18

CADTH

Appendix B: CADTH Biosimilars Clinician(s) Input

Biosimilars Clinician Input Template for CADTH pCODR Program

Name of the Biosimilar and Indication	**Mvasi / Metastatic Colorectal Cancer / Non-Small Cell Lung Cancer Biosimilar**
Do you have experience with prescribing the biosimilar under review?	**No**

Introduction

Biologic drugs come from living organisms or from their cells and are often made using biotechnology.

They are used to treat diseases and medical conditions including anemia, diabetes, inflammatory bowel disease, psoriasis, rheumatoid arthritis, hormone deficiency, and some forms of cancer.

A biosimilar is a drug demonstrated to be highly similar to a biologic drug (known as the reference biologic drug) that was already authorized for sale by the regulatory body, Health Canada. Biosimilars are approved based on having no clinically meaningful differences compared with the reference biologic drug product in terms of safety, purity, and efficacy. Biosimilars may enter the market after the expiry of reference biologic drug patents and data protection.

To help inform the advice that you provide to CADTH and that will be shared with the pan-Canadian Pharmaceutical Alliance and participating jurisdictions making a funding decision, please consider the following:

A. Awareness About Biosimilars

1. How familiar are you with biosimilars and how they are approved in Canada? (Please specify: very familiar, somewhat familiar, not at all familiar.) If you are familiar with biosimilars, how was this information obtained (e.g., government or not-for-profit organization, industry, general website, other [please specify])?

- At least somewhat familiar.
- It can be difficult to adjudicate the efficacy of a biosimilar – data to demonstrate equivalency is not held to the same standard at which the parent drug is evaluated (biosimilars could also be better than the parent drug).
- Comfort in using biosimilars also may stem from similar efficacies observed of drugs in the same class → e.g. nivolumab/pembrolizumab and cetuximab/panitumumab → not the same drug (same drug class) but are often considered more or less equivalent by clinicians.

2. Are you aware whether there are other brands of biosimilars that may be available to treat the requested indication(s)? If yes, please specify.

No – although the DAC agreed that there may be others that they are unaware of.

B. Initiating a Patient on a Biosimilar

1. In which circumstances would you initiate a patient on a biosimilar? Please describe if there are considerations with initiating a biosimilar in the adjuvant or metastatic setting.

- In general, the DAC agreed that they would be willing to initiate a patient or switch a patient to a biosimilar as long as there is rigorous evidence suggesting similar pharmacology (bioequivalence) & a transparent approval process. They would use Mvasi the same way as bevacizumab (same for both the adjuvant and metastatic setting).
- The DAC noted that they are unsure if Mvasi has demonstrated bioequivalence for this indication.
- The decision to use a biosimilar is often not up to the clinician → e.g. hospital decision.

C. Switching a Patient to a Biosimilar

1. In which circumstances would you switch a patient to a biosimilar from the reference biologic drug? Please describe if there are considerations with switching a patient to a biosimilar in the adjuvant or metastatic setting.

See above

D. About the Biosimilar Under Review

1. As a biosimilar is considered to be effective and safe by the regulatory body and using a biosimilar could help to increase access by other patients to new therapies, would this information be a factor in your prescribing decision?

Yes

2. What information might be helpful to inform your decision to initiate or switch to a biosimilar? Please describe if there were any benefits or side effects experienced with the biosimilar.

See above

E. Accessibility Considerations

1. Are you aware whether there is a patient support program for the biosimilar under review; if so, please describe the program for the biosimilar (e.g., administration, testing, monitoring)?

The DAC is not aware of any patient support program.

2. Please describe whether there are any potential barriers to prescribing a biosimilar.

Besides lack of evidence, there may be differences in premedication, but it will depend on the biosimilar.

F. Implementation Questions

The Ministries of Health and provincial cancer programs across Canada are concerned about the sustainability of high-quality cancer control services. The rising cost of cancer drugs is becoming a major challenge to the sustainability of cancer care funding. While tremendous progress has been made in recent years in the cancer drug system, more is needed to be done to ensure innovative treatments are available to patients, while ensuring value for money for the public.

If applicable, we will be seeking your clinical opinion on the following implementation issues, if and when the new treatment is reimbursed. Your responses would be taken into consideration, amongst other factors, when Ministries of Health and provincial cancer programs make their final funding decisions.

1. The reference biologic drug (Avastin) has not been reviewed by pCODR for the requested funding request for the biosimilar drug (Mvasi). Bevacizumab (Avastin) is not funded in the non-small cell lung cancer (NSCLC) setting in Canada.

    1.1. In clinical practice, would you use the biosimilar bevacizumab (Mvasi) for indications approved by Health Canada (e.g., NSCLC) that have not been reviewed by pCODR?

    1.2. In clinical practice, would you want to extend the use of the biosimilar bevacizumab (Mvasi) to indications not approved by Health Canada that were reviewed by pCODR (e.g., Ovarian Cancer [Full Indication: In combination with paclitaxel and carboplatin for the front-line treatment of epithelial ovarian, fallopian tube or primary peritoneal cancer patients with high risk of relapse (stage III sub-optimally debulked, or stage III unresectable, or stage IV patients], Cervical Cancer)?

- Yes (for both), although this is a difficult question to answer – will need input from all relevant disease site groups.
- If there is demonstrated bioequivalence, it is reasonable to use the biosimilar in all the indications approved for the parent drug.

pCODR Clinician Conflict of Interest Declarations

Note: Each registered clinician must complete their own separate pCODR Clinician Conflict of Interest Declarations Template even if the submission is made jointly.

Name of registered clinician: Stephen Welch

Name of drug and indication under review: Mvasi/CRC

Conflict of Interest Declarations

To maintain the objectivity and credibility of the pCODR process, all participants in the pCODR review process must disclose any conflicts of interest. A registered clinician must declare any potential conflicts of interest that may influence or have the appearance of influencing the information submitted. Conflict of interest declaration is requested for transparency — it does not negate or preclude the use of the clinician input.

Examples of conflicts of interest include, but are not limited to:

- financial support from the pharmaceutical industry or other entities e.g., educational or research grants, honoraria, gifts, and salary;
- affiliations or personal or commercial relationships with drug manufacturers or other interest groups.

Section A: Payment Received

1. **Have you received any payments over the previous two years from any company or organization that may have direct or indirect interest in the drug under review?**

   ☒ Yes ☐ No

   If no, please go to Section B.

2. **What form of payment did you receive?** (Check all that apply.)

☐	Advisory role (e.g., advisory boards, HTA submission advice)	☐	Program or Operating Funding (e.g., website)
☐	Conference attendance	☐	Research/educational grants
☐	Royalties	☐	Travel grants
☐	Gifts	☐	Sponsorship of Events
☒	Honoraria		
☐	Other, please specify: Click here to enter text.		

3. **Please provide the names of companies and organizations and the amounts of the payments in the box below.**

Amgen – Honoraria [redacted] ESMO 2016 Consultant [redacted]

Section B: Holdings or Other Interests

Have you received or is it in possession of stocks or options of more than $10,000 (excluding mutual funds) for organizations that may have a direct or indirect interest in the drug under review? If yes, please list in the table below.

Click here to enter text.

Section C: Affiliations, personal or commercial relationships

Do you have personal or commercial relationships either with a drug or health technology manufacturer (including such manufacturer's parent corporation, subsidiaries, affiliates and associated corporations) or other interest groups? If yes, please provide the names of the companies and organizations and outline the nature of these relationships in the table below.

Click here to enter text.

I hereby certify that I have disclosed all relevant information with respect to any matter involving a Party that may place me in a real, potential or perceived conflict of interest situation.

Date: September 22, 2017

Name: Stephen Welch

Signature: 

pCODR Clinician Conflict of Interest Declarations

Note: Each registered clinician must complete their own separate pCODR Clinician Conflict of Interest Declarations Template even if the submission is made jointly.

Name of registered clinician: Jim Biagi

Name of drug and indication under review: Mvasi/CRC

Conflict of Interest Declarations

To maintain the objectivity and credibility of the pCODR process, all participants in the pCODR review process must disclose any conflicts of interest. A registered clinician must declare any potential conflicts of interest that may influence or have the appearance of influencing the information submitted. Conflict of interest declaration is requested for transparency — it does not negate or preclude the use of the clinician input.

Examples of conflicts of interest include, but are not limited to:

- financial support from the pharmaceutical industry or other entities e.g., educational or research grants, honoraria, gifts, and salary;
- affiliations or personal or commercial relationships with drug manufacturers or other interest groups.

Section A: Payment Received

1. **Have you received any payments over the previous two years from any company or organization that may have direct or indirect interest in the drug under review?**

   ☐ Yes ☒ No

   If no, please go to Section B.

2. **What form of payment did you receive?** (Check all that apply.)

   ☐ Advisory role (e.g., advisory boards, HTA submission advice)
   ☐ Conference attendance
   ☐ Royalties
   ☐ Gifts
   ☐ Honoraria
   ☐ Other, please specify: Click here to enter text.
   ☐ Program or Operating Funding (e.g., website)
   ☐ Research/educational grants
   ☐ Travel grants
   ☐ Sponsorship of Events

3. **Please provide the names of companies and organizations and the amounts of the payments in the box below.**

Click here to enter text.

Section B: Holdings or Other Interests

Have you received or is it in possession of stocks or options of more than $10,000 (excluding mutual funds) for organizations that may have a direct or indirect interest in the drug under review? If yes, please list in the table below.

No

Section C: Affiliations, personal or commercial relationships

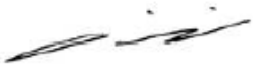
Do you have personal or commercial relationships either with a drug or health technology manufacturer (including such manufacturer's parent corporation, subsidiaries, affiliates and associated corporations) or other interest groups? If yes, please provide the names of the companies and organizations and outline the nature of these relationships in the table below.

No

I hereby certify that I have disclosed all relevant information with respect to any matter involving a Party that may place me in a real, potential or perceived conflict of interest situation.

Date: October 12 2018

Name: Jim Biagi

Signature: 

pCODR Clinician Conflict of Interest Declarations

Note: Each registered clinician must complete their own separate pCODR Clinician Conflict of Interest Declarations Template even if the submission is made jointly.

Name of registered clinician: Dr. Erin Kennedy

Name of drug and indication under review: Mvasi/CRC

Conflict of Interest Declarations

To maintain the objectivity and credibility of the pCODR process, all participants in the pCODR review process must disclose any conflicts of interest. A registered clinician must declare any potential conflicts of interest that may influence or have the appearance of influencing the information submitted. Conflict of interest declaration is requested for transparency — it does not negate or preclude the use of the clinician input.

Examples of conflicts of interest include, but are not limited to:

- financial support from the pharmaceutical industry or other entities e.g., educational or research grants, honoraria, gifts, and salary;
- affiliations or personal or commercial relationships with drug manufacturers or other interest groups.

Section A: Payment Received

1. **Have you received any payments over the previous two years from any company or organization that may have direct or indirect interest in the drug under review?**

   ☐ Yes ☑ No

   If no, please go to Section B.

2. **What form of payment did you receive?** (Check all that apply.)

   ☐ Advisory role (e.g., advisory boards, HTA submission advise)
   ☐ Conference attendance
   ☐ Royalties
   ☐ Gifts
   ☐ Honoraria
   ☐ Other, please specify: Click here to enter text.
   ☐ Program or Operating Funding (e.g., website)
   ☐ Research/educational grants
   ☐ Travel grants
   ☐ Sponsorship of Events

3. **Please provide the names of companies and organizations and the amounts of the payments in the box below.**

Click here to enter text. None

Section B: Holdings or Other Interests

Have you received or is it in possession of stocks or options of more than $10,000 (excluding mutual funds) for organizations that may have a direct or indirect interest in the drug under review? If yes, please list in the table below.

Click here to enter text. None

Section C: Affiliations, personal or commercial relationships

Do you have personal or commercial relationships either with a drug or health technology manufacturer (including such manufacturer's parent corporation, subsidiaries, affiliates and associated corporations) or other interest groups? If yes, please provide the names of the companies and organizations and outline the nature of these relationships in the table below.

Click here to enter text. None

I hereby certify that I have disclosed all relevant information with respect to any matter involving a Party that may place me in a real, potential or perceived conflict of interest situation.

Date: Click here to enter text. May 3 / 2018

Name: Click here to enter text. Erin Kennedy

Signature: Click here to enter text.

CADTH

Biosimilars Clinician Input Template for CADTH pCODR Program

Name of the Biosimilar and Indication	**Mvasi; colorectal cancer and possibly nonsmall cell lung cancer**
Do you have experience with prescribing the biosimilar under review?	**No**

Introduction

Biologic drugs come from living organisms or from their cells and are often made using biotechnology. They are used to treat diseases and medical conditions including anemia, diabetes, inflammatory bowel disease, psoriasis, rheumatoid arthritis, hormone deficiency, and some forms of cancer.

A biosimilar is a drug demonstrated to be highly similar to a biologic drug (known as the reference biologic drug) that was already authorized for sale by the regulatory body, Health Canada. Biosimilars are approved based on having no clinically meaningful differences compared with the reference biologic drug product in terms of safety, purity, and efficacy. Biosimilars may enter the market after the expiry of reference biologic drug patents and data protection. To help inform the advice that you provide to CADTH and that will be shared with the pan-Canadian Pharmaceutical Alliance and participating jurisdictions making a funding decision, please consider the following:

A. Awareness About Biosimilars

1. How familiar are you with biosimilars and how they are approved in Canada? (Please specify: very familiar, somewhat familiar, not at all familiar.) If you are familiar with biosimilars, how was this information obtained (e.g., government or not-for-profit organization, industry, general website, other [please specify])?

Somewhat familiar; education by advisory boards of several different companies.

2. Are you aware whether there are other brands of biosimilars that may be available to treat the requested indication(s)? If yes, please specify.

Another branded product has been available for many years.

B. Initiating a Patient on a Biosimilar

1. In which circumstances would you initiate a patient on a biosimilar? Please describe if there are considerations with initiating a biosimilar in the adjuvant or metastatic setting.

In colorectal cancer, for Mvasi, only in the metastatic setting in first line; for the same sort of pts that I would prescribe the branded product.

C. Switching a Patient to a Biosimilar

1. In which circumstances would you switch a patient to a biosimilar from the reference biologic drug? Please describe if there are considerations with switching a patient to a biosimilar in the adjuvant or metastatic setting.

Some clinicians are against switching during the course of Rx; I am OK to switch once the biosimilar becomes available.

D. About the Biosimilar Under Review

1. As a biosimilar is considered to be effective and safe by the regulatory body and using a biosimilar could help to increase access by other patients to new therapies, would this information be a factor in your prescribing decision?

Yes; we should strive to be as efficient with our resources as possible so as to stretch them.

2. What information might be helpful to inform your decision to initiate or switch to a biosimilar? Please describe if there were any benefits or side effects experienced with the biosimilar.

Benefits are the reduced cost to the health care system and more pts can be treated with various new, expensive drugs. The side effects I expect to be the same as the branded product; and quality control can be left to Health Canada.

E. Accessibility Considerations

1. Are you aware whether there is a patient support program for the biosimilar under review; if so, please describe the program for the biosimilar (e.g., administration, testing, monitoring)?

Currently unaware of this.

2. Please describe whether there are any potential barriers to prescribing a biosimilar.

Not by me. As long as it is OK'd by Health Canada, I am ok with it.

F. Implementation Questions

The Ministries of Health and provincial cancer programs across Canada are concerned about the sustainability of high-quality cancer control services. The rising cost of cancer drugs is becoming a major challenge to the sustainability of cancer care funding. While tremendous progress has been made in recent years in the cancer drug system, more is needed to be done to ensure innovative treatments are available to patients, while ensuring value for money for the public.

If applicable, we will be seeking your clinical opinion on the following implementation issues, if and when the new treatment is reimbursed. Your responses would be taken into consideration, amongst other factors, when Ministries of Health and provincial cancer programs make their final funding decisions.

1. The reference biologic drug (Avastin) has not been reviewed by pCODR for the requested funding request for the biosimilar drug (Mvasi). Bevacizumab (Avastin) is not funded in the non-small cell lung cancer (NSCLC) setting in Canada.

    1.1. In clinical practice, would you use the biosimilar bevacizumab (Mvasi) for indications approved by Health Canada (e.g., NSCLC) that have not been reviewed by pCODR?

    1.2. In clinical practice, would you want to extend the use of the biosimilar bevacizumab (Mvasi) to indications not approved by Health Canada that were reviewed by pCODR (e.g., Ovarian Cancer [Full Indication: In combination with paclitaxel and carboplatin for the front-line treatment of epithelial ovarian, fallopian tube or primary peritoneal cancer patients with high risk of relapse (stage III sub-optimally debulked, or stage III unresectable, or stage IV patients], Cervical Cancer)?

- Yes I would, based on the evidence
- Yes, I think one can extrapolate

CADTH

Appendix: Clinician Group Conflict of Interest Declaration

Please Note: Each registered clinician must complete their own separate pCODR Clinician Conflict of Interest Declarations Template even if the submission is made jointly.

Name of registered clinician:	Mark D Vincent
Name of drug and indication under review:	Mvasi Advanced Nonsmall cel lung cancer (possibly colorectal cancer)

Conflict of Interest Declarations

To maintain the objectivity and credibility of the pCODR process, all participants in the pCODR review process must disclose any conflicts of interest. A registered clinician must declare any potential conflicts of interest that may influence or have the appearance of influencing the information submitted. Conflict of interest declaration is requested for transparency — it does not negate or preclude the use of the clinician input.

Examples of conflicts of interest include, but are not limited to:

- financial support from the pharmaceutical industry or other entities e.g., educational or research grants, honoraria, gifts, and salary;
- affiliations or personal or commercial relationships with drug manufacturers or other interest groups.

Section A: Payment Received

1. Have you received any payments over the previous two years from any company or organization that may have direct or indirect interest in the drug under review?

   x Yes
   □ No

   If no, please go to Section B

2. What form of payment did you receive? (Check all that apply.)

x	Advisory role (e.g., advisory boards, HTA submission advice)	□	Program or Operating Funding (e.g., website)
x	Conference attendance	x	Research/educational grants
□	Royalties	□	Travel grants
□	Gifts	□	Sponsorship of Events
x	Honoraria	□	Other, please specify: _____

3. Please provide the names of companies and organizations and the amounts of the payments in the box below.

Amgen Canada (about [redacted] in total); Hoffmann La Roche Canada (about [redacted] in total)

Section B: Holdings or Other Interests

1. Have you received or is it in possession of stocks or options of more than $10,000 (excluding mutual funds) for organizations that may have a direct or indirect interest in the drug under review? If yes, please list in the table below.

No

Section C: Affiliations, personal or commercial relationships

2. Do you have personal or commercial relationships either with a drug or health technology manufacturer (including such manufacturer's parent corporation, subsidiaries, affiliates and associated corporations) or other interest groups? If yes, please provide the names of the companies and organizations and outline the nature of these relationships in the table below.

No

I hereby certify that I have disclosed all relevant information with respect to any matter involving a Party that may place me in a real, potential or perceived conflict of interest situation.

Date: October 12, 2018 Name: Mark D Vincent Signature: Mvincent

Appendix C: References

Manufacturer's references:

1. Markus R, Chow V, Pan Z, Hanes V. A phase I, randomized, single-dose study evaluating the pharmacokinetic equivalence of biosimilar ABP 215 and bevacizumab in healthy adult men. *Cancer Chemother Pharmacol.* 2017;80(4):755-763.
2. Thatcher N, Thomas M, Ostoros G, Pan Z, Goldschmidt JH, Hanes V. Secondary efficacy results from a phase 3 study comparing efficacy and safety of biosimilar candidate ABP 215 with bevacizumab in patients with non-squamous non-small cell lung cancer (NSCLC). *Ann Oncol.* 2016;27(Suppl 6):vi411-vi415.
3. Thatcher N, Thomas M, Ostoros G, et al. Randomized, double-blind, phase 3 study comparing biosimilar candidate ABP 215 with bevacizumab in patients with non-squamous NSCLC. *J Thorac Oncol.* 2017;15(1 Suppl):S902-S903.
4. Thatcher N, Thomas M, Paz-Ares L, et al. Randomized, double-blind, phase 3 study evaluating efficacy and safety of ABP 215 compared with bevacizumab in patients with non-squamous NSCLC. *J Clin Oncol.* 2016;34(15 Suppl):9095.
5. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45(2):228-247.
6. Clarke JM, Wang X, Ready NE. Surrogate clinical endpoints to predict overall survival in non-small cell lung cancer trials-are we in a new era? *Transl Lung Cancer Res.* 2015;4(6):804-808.

CADTH references:

1. Avastin (bevacizumab): 100 mg and 400 mg vials (25 mg/mL solution for injection) [product monograph]. Mississauga (ON): Hoffmann-La Roche Limited; 2018 Jun 6: https://pdf.hres.ca/dpd_pm/00045825.PDF. Accessed 2018 Nov 19.
2. Mvasi (bevacizumab): 100 mg and 400 mg vials (25 mg/mL solution for injection) [product monograph]. Mississauga (ON): Amgen Canada Inc.; 2018 Apr 30: https://pdf.hres.ca/dpd_pm/00045004.PDF. Accessed 2018 Nov 19.
3. DeltaPA. Ottawa (ON): IQVIA; 2018: https://www.iqvia.com/. Accessed 2018 Nov 19.
4. Switching from Avastin or other bevacizumab biosimilars to biosimilar Mvasi: clinical effectiveness. *(CADTH Rapid response report: reference list).* Ottawa (ON): CADTH; 2018: https://www.cadth.ca/sites/default/files/pdf/htis/2018/RA0982%20Bevacizumab%20Switching%20Final.pdf. Accessed 2018 Dec 11.