**Reimbursement Review**

**Pharmaceuticals With Anticipated Comparable Efficacy and Safety (PACES) Tailored Review Sponsor Submission Template**

**Instructions for Sponsors**

Background

A pharmaceuticals with anticipated comparator efficacy and safety (PACES) tailored review consists of CDA-AMC conducting an appraisal of the clinical evidence and economic evaluation submitted by the sponsor using this template. Information from the sponsor’s submission will be validated and critically appraised by CDA-AMC.

Please read the instructions below and consult the recommended documentation before completing the template. If you have any questions regarding the application process, please email [requests@cda-amc.ca](mailto:requests@cda-amc.ca) with the complete details of your question(s).

Roles and Responsibilities for Publication

All Reimbursement Review reports are posted on the CDA-AMC website for anyone to access and review.

The sponsor is responsible for the quality, currency, propriety, and accuracy of the information provided to CDA-AMC for publication via this tailored review submission template, and that the content complies with both [Canadian copyright law](https://laws-lois.justice.gc.ca/eng/acts/C-42/Index.html) and current Ontario accessibility guidelines for posting information online (refer to section on accessibility below).

Should the tailored review submission be accepted for review and publication, the sponsor will have the opportunity to review the report for any inaccuracies or confidential information not in the public domain before posting on the CDA-AMC website.

Accessibility for Ontarians

In keeping with the [*Accessibility for Ontarians with Disabilities Act*](https://www.ontario.ca/laws/statute/05a11) (AODA), all public documents must now be compliant with Ontario’s accessibility guidelines to ensure access for people who experience disabilities. MS Word (and other Microsoft software) provides an [Accessibility Checker](https://support.microsoft.com/en-us/office/rules-for-the-accessibility-checker-651e08f2-0fc3-4e10-aaca-74b4a67101c1) for identifying and repairing accessibility issues, which is located under the **Review** tab and **Check Accessibility** sub-tab.

When completing your submission:

* Reuse the existing AODA-compliant tables within this template if more tables are required. If using your own tables, ensure that all columns and rows have a header. Do not leave blank cells within tables.
* Include 1 to 2 lines of alternative text (alt-text) to describe any figures or images included within this document.
* When using figures and graphs, colour should not be used as the sole method for conveying content or distinguishing visual elements.

Before Completing the Template

Please review the following documents to ensure an understanding of our procedures and submission guidelines:

* [Procedures for Reimbursement Reviews](https://www.cda-amc.ca/sites/default/files/Drug_Review_Process/Drug_Reimbursement_Review_Procedures.pdf)
* Pharmaceutical Review Updates for any applicable information.

Completing the Template

General Guidelines

Complete all sections of the template using 9-point Arial font type in text and 9-point Arial font in tables. Do not alter the page margin settings. Include figure and table numbers and provide a list of figures and a list of tables after the table of contents. Data should reflect the results reported in the clinical study report(s) whenever possible. **The total length of the Background, Sponsor’s Summary of the Systematic Review Evidence, and Sponsor’s Summary of the Indirect Evidence sections (excluding the tables of contents, abbreviations list, appendices, and reference list), cannot exceed 15 pages.**

When the template is complete, delete this cover page with the instructions, the record of updates section, and all red font instructions throughout the template. Save the completed template as a Word document.

Completing References

Provide clear references to source documentation used (including citations and corresponding table and figure numbers from data sources) when completing the template. In-text citations to sponsor references must be referenced numerically in order of appearance using superscript numbers. The sponsor must provide an RIS file containing the references used in the report. An RIS file is a standardized bibliographic format that enables citation management programs to exchange documents. References must be provided at the end of the document in the References section.

Background

In this section the sponsor is required to summarize key background information regarding the drug under review and the condition for which the drug under review is indicated. Please ensure that statements are appropriately referenced. Appendix 1 accompanies this section and must be completed.

Sponsor’s Summary of the Systematic Review Evidence

In this section the sponsor is required to summarize the results from a systematic literature review. The literature review must be conducted and reported in accordance with the instructions provided within this template. Appendices 2 to 7 accompany this section and must be completed.

Sponsor’s Summary of the Indirect Evidence

In this section the sponsor must summarize all indirect comparisons that have been included in the application. In addition to this summary, the sponsor must provide the complete technical reports for the indirect comparisons as described in the [Procedures for Reimbursement Reviews](https://www.cda-amc.ca/sites/default/files/Drug_Review_Process/Drug_Reimbursement_Review_Procedures.pdf). If no indirect treatment comparisons are being included in the application, explain within the template why an indirect comparison is not relevant for the review (i.e., do not delete the section if there are no data available). Appendix 8 accompanies this section and must be completed.

Pharmacoeconomic Evaluation

This section is reserved for the CDA-AMC review of the sponsor’s economic evaluation. In Appendix 9, which accompanies this section, the sponsor must summarize the treatment information, model information, data sources, and results of their cost minimization analysis. Please note that this appendix is to be completed in addition to the Technical Report and Excel workbook and other items required per the [Procedures for Reimbursement Reviews](https://www.cda-amc.ca/sites/default/files/Drug_Review_Process/Drug_Reimbursement_Review_Procedures.pdf) (refer to the Cost-Minimization Analysis section within the Pharmacoeconomic Submission section).

Record of Updates to Template

|  |  |  |
| --- | --- | --- |
| **Version** | **Date** | **Summary of revisions** |
| 1 | February 27, 2025 | Original version posted |

Table of Contents

Please update the Table of Contents prior to submitting the application.

[Record of Updates to Template 4](#_Toc190965924)

[List of Tables 6](#_Toc190965925)

[List of Figures 6](#_Toc190965926)

[Abbreviations 7](#_Toc190965927)

[Background 8](#_Toc190965928)

[Sponsor’s Summary of Disease Background and Current Management 8](#_Toc190965929)

[Sponsor’s Summary of the Systematic Review Evidence 9](#_Toc190965930)

[Objective and Methods 9](#_Toc190965931)

[Included Studies 9](#_Toc190965932)

[Results 14](#_Toc190965933)

[Sponsor’s Summary of the Indirect Evidence 16](#_Toc190965934)

[Description of Indirect Treatment Comparison(s) 17](#_Toc190965935)

[Results 17](#_Toc190965936)

[Pharmacoeconomic Evaluation 19](#_Toc190965937)

[Appendix 1: Key Characteristics of Treatment Options 20](#_Toc190965938)

[Appendix 2: Systematic Review Procol and Literature Search Strategy 21](#_Toc190965939)

[Review Protocol 21](#_Toc190965940)

[Literature Search and Study Selection 22](#_Toc190965941)

[Appendix 3: List of Excluded Studies 25](#_Toc190965942)

[Appendix 4: Methods of the Studies in the Systematic Review 26](#_Toc190965943)

[Additional Eligibility Criteria 26](#_Toc190965944)

[Description of Outcome Measures 26](#_Toc190965945)

[Statistical Analysis 26](#_Toc190965946)

[Appendix 5: Exposure to Other Treatments for Studies in the Systematic Review 28](#_Toc190965947)

[Appendix 6: Additional Efficacy Results for the Studies in the Systematic Review 29](#_Toc190965948)

[Appendix 7: Detailed Harms Results for the Studies in the Systematic Review 30](#_Toc190965949)

[Appendix 8: Detailed Methods for the Indirect Treatment Comparison 31](#_Toc190965950)

[Study Selection and Review Methods 31](#_Toc190965951)

[Indirect Comparison Analysis Methods 31](#_Toc190965952)

[Appendix 9: Summary of Sponsor’s Economic Evaluation 34](#_Toc190965953)

[References 36](#_Toc190965954)

List of Tables

Please update the List of Tables prior to submitting the application.

[Table 1: Application Submitted for Review 8](#_Toc190965955)

[Table 2: Details of Included Studies 9](#_Toc190965956)

[Table 3: Summary of Outcomes Relevant to the Systematic Review 11](#_Toc190965957)

[Table 4: Analysis Populations of Study 1 and Study 2 12](#_Toc190965958)

[Table 5: Summary of Baseline Characteristics of Study 1 and Study 2 13](#_Toc190965959)

[Table 6: Patient Disposition for Study 1 and Study 2 13](#_Toc190965960)

[Table 7: Exposure to Study Treatment for Study 1 and Study 2 (Sample Table) 14](#_Toc190965961)

[Table 8: Summary of Key Efficacy Results 15](#_Toc190965962)

[Table 9: Assessment of Homogeneity (Sample Table) 17](#_Toc190965963)

[Table 10: ITC Sample Data Table for Continuous Outcomes (e.g., Summary of NMA Results for Efficacy Results, [Treatment] Versus Comparators) 18](#_Toc190965964)

[Table 11: ITC Sample Data Table for Dichotomous Outcomes (e.g., Summary of NMA Results for Efficacy Results, [Treatment] Versus Comparators) 18](#_Toc190965965)

[Table 12: Key Characteristics of Drug 1, Drug 2, etc. 20](#_Toc190965966)

[Table 13: Inclusion Criteria for the Systematic Review 22](#_Toc190965967)

[Table 14: Excluded Studies 25](#_Toc190965968)

[Table 15: Statistical Analysis of Efficacy End Points 27](#_Toc190965969)

[Table 16: Sample Table for Subsequent Treatment 28](#_Toc190965970)

[Table 17: Summary of Key Harms Results 30](#_Toc190965971)

[Table 18: Study Selection Criteria and Methods for Indirect Comparisons 31](#_Toc190965972)

[Table 19: Indirect Comparison Analysis Methods 32](#_Toc190965973)

[Table 20: Key Components of the Sponsor’s Economic Evaluation 34](#_Toc190965974)

List of Figures

Please update the List of Figures prior to submitting the application.

**No table of figures entries found.**

Abbreviations

Examples of commonly used abbreviations are provided below. Please add or remove from the list as needed.

**AE** adverse event

**CI** confidence interval

**DB** double blind

**FAS** full analysis set

**ITT** intention-to-treat population

**PP** per-protocol

**RCT** randomized controlled trial

**RR** relative risk

**SAE** serious adverse event

**SD** standard deviation

**WDAE** withdrawal due to adverse event

Background

Sponsor’s Summary of Disease Background and Current Management

Application Summary

Table 1: Application Submitted for Review

| Item | Description |
| --- | --- |
| **Drug (product)** | Non-proprietary name (Brand Name), strength, dosage form(s), route of administration |
| **Sponsor** |  |
| **Health Canada indication** | Health Canada indication as per product monograph (abbreviate if necessary); if pre-NOC submission state: Proposed: |
| **Sponsor’s reimbursement request** | Ensure this is consistent throughout all components of the application  If same as indication, state “As per indication.” |
| **Health Canada approval status** | NOC, NOC/c, Under review (pre-NOC) |
| **Health Canada review pathway** | Standard, priority review, advance consideration under NOC/c, other (please specify) |
| **NOC date** | If NOC received, state: Month day, year  If pre-NOC submission, state: anticipated Month day, year |

NOC = Notice of Compliance. Abbreviations must be listed under the table in alphabetical order.

Disease Background

Provide a brief description of the disease. Please ensure the following information is reported with references (as applicable): incidence and prevalence (in Canada, if available), signs and symptoms, natural history, disease staging, and survival/mortality.

[Start typing report details here]

Diagnosis of the Condition

Briefly describe any diagnostic tests that would be required or recommended to identify the patient population that could be eligible for treatment with the drug under review. This should include the name, analyte, and rationale for each diagnostic test. Please note if there are any confirmed or anticipated statements in the Canadian product monograph regarding specific diagnostic technology that is recommended for the drug under review.

Please provide a brief overview of the following, if applicable:

* + any provinces or territories where there is likely to be limited access to the diagnostic testing requirements for the indication(s) of interest at the time CDA-AMC’s review is targeted to be completed
  + any initiatives being undertaken by the sponsor and/or others to increase the availability of the diagnostic test in Canada

[Start typing report details here]

Current Management and Place in Therapy of the Drug Under Review

Current Treatment Options

Describe current therapeutic approaches (including pharmacological and non-pharmacological interventions) in Canada for the condition of interest.

* + Cite clinical practice guidelines as appropriate.
  + Describe the treatment goals (such as prolonging life, delaying disease progression, improving symptoms, minimizing side effects, improving quality of life, increasing the patient’s ability to maintain employment, maintain independence, reducing burden on caregivers, etc.).
  + Identify all drug therapies that are currently available for the target population. If some drugs are not listed on public formularies, please describe how they can be accessed by the patient.

[Start typing report details here]

Key characteristics of [drug under review] are summarized with other treatments available for [condition under review] in Appendix 1.

If there are relevant comparators (see guidance in Appendix 1 for a definition of relevant comparators) for which no clinical evidence has been submitted comparing it with the drug under review, include a paragraph here explaining the rationale for the lack of submitted evidence.

[Start typing report details here]

Impact of the Drug Under Review on Treatment Options

Please briefly describe the potential impact of the introduction of the drug under review on currently reimbursed treatments for the indication, including which treatments are expected to be displaced.

[Start typing report details here]

Sponsor’s Summary of the Systematic Review Evidence

Objective and Methods

The objective is to perform a systematic review of the beneficial and harmful effects of [state non-proprietary drug name] for [state the indication of interest] versus relevant comparators in clinical practice in Canada.

Refer to Appendix 2 for details on the systematic review protocol, literature search strategy, and study selection process and refer to Appendix 3 for the list of excluded studies.

Included Studies

Table 2: Details of Included Studies

| Item | Study Name | Study Name |
| --- | --- | --- |
| Study design and population | | |
| **Study design** | Briefly describe (e.g., phase 3, double-blind, placebo-controlled RCT) | Briefly describe (e.g., phase 3, double-blind, placebo-controlled RCT) |
| **Locations** | List number of sites and state the countries/regions where the trial was conducted (include the number of sites in Canada) | List number of sites and state the countries/regions where the trial was conducted |
| **Patient enrolment Dates:** | **Start date:** State date  **End date:** State date | **Start date:** State date  **End date:** State date |
| **Randomized (N)** | State the total N and include the sample size in each treatment group. | State the total N and include the sample size in each treatment group. |
| **Inclusion criteria** | Please list key criteria only | Please list key criteria only |
| **Exclusion criteria** | Please list key criteria only | Please list key criteria only |
| Drugs | | |
| **Intervention** | State the drug, dosage, frequency of administration, route of administration, duration | State the drug, dosage, frequency of administration, route of administration, duration |
| **Comparator(s)** | For each comparator: state the drug, dosage, frequency of administration, route of administration, duration of treatment | For each comparator: state the drug, dosage, frequency of administration, route of administration, duration of treatment |
| Duration | | |
| **Screening phase** | Specify duration | Specify duration |
| **Run-in phase** | Specify duration (delete if not applicable) | Specify duration (delete if not applicable) |
| **Treatment phase** | Specify duration | Specify duration |
| **Follow-up phase** | Specify duration | Specify duration |
| Outcomes | | |
| **Primary end point** | State the primary endpoint including the timeframe (e.g., through 24 weeks) | State the primary endpoint including the timeframe (e.g., through 24 weeks) |
| Publication status | | |
| **Publications** | State reference(s) to journal publications Author et al. Yearcitation | State reference(s) to journal publications  Author et al. Yearcitation |

Abbreviations must be listed under the table in alphabetical order. For example, CI = confidence interval; OR = odds ratio

Source: For all tables reporting information from included studies, indicate data source including citation (and corresponding table number[s] in the clinical study report where applicable). Data should reflect the results reported in the clinical study report(s) whenever possible.

* For each study the following information should also be presented:
  + Study objectives
  + Randomization, whether randomization was stratified
  + Data cut-off dates
  + If applicable, briefly describe key design features (e.g., adaptive design, enrichment design, withdrawal design, cross-over design) and key points related to those features (e.g., duration of washout period between treatment periods in a cross-over study).
  + For studies with a run-in/screening period, briefly describe its purpose.
* If appropriate, include a figure showing the duration and characteristics of the different phases of the study (e.g., run-in period, treatment period, follow-up).

[Start typing report details here]

Eligibility Criteria

Delete this section if not needed.

* + Identify any important differences in inclusion and exclusion criteria between the studies.
  + If there are additional eligibility criteria that are important to consider when interpreting the results (beyond those in Table 3), they may be reported in Appendix 4.

[Start typing report details here]

Interventions

Briefly describe important details of the interventions employed in the included trials that are not already in the Details of Included Studies table (delete this section if not needed). This may include:

* A description of the titration schedule and the criteria used for determining the titration schedule should be included (e.g., fixed schedule or titration to target).
* For non-oral medications or medications requiring a device for administration (e.g., insulin pen, auto-injector, inhalation device), details related to the device, training, and administration should be included, examples of which are provided below:
  + - For an injection, details may include whether the injection was self-administered or administered by study personnel at a study visit.
    - For an infusion, please include the infusion duration and indicate in what setting the infusion will be administered (i.e., hospital or infusion center).
    - If a device was used, please describe the training that was given initially and at each study visit. Please indicate if the device that was used is the same one that is or will be available in Canada.
* If the trial is blinded, indicate the use of placebos, double-dummy controls, and provide a brief description of the placebo including any methods to match administration and avoid unblinding.
* Include any criteria for rescue medication use where applicable, along with dosing schedules and maximum dosages permitted. Describe any stopping criteria for the intervention if relevant.
* Important permitted and/or prohibited concomitant medications and co-interventions.

[Start typing report details here]

Outcomes

Detailed descriptions of relevant outcome measures are presented in Appendix 4.

The summary table below is required for all applications. When identifying primary and secondary endpoints, include a superscript letter and footnote identifying which endpoints were adjusted for multiple comparisons in the statistical analyses.

Table 3: Summary of Outcomes Relevant to the Systematic Review

| Outcome measure | Timepoint | Study 1 | Study 2 |
| --- | --- | --- | --- |
| List outcome 1 | Please be specific (e.g., at 24 weeks; through 24 weeks) | Please state as:   * Primarya * Key secondarya * Secondary * Tertiary * Exploratory * If the outcome listed in the row was used in some studies, but not others state ‘not applicable’ for those that did not include the outcome.   Include a footnote to identify endpoints where statistical testing was adjusted for multiple comparisons | Please state as:   * Primarya * Key secondarya * Secondary * Tertiary * Exploratory * If the outcome listed in the row used in some studies, but not others state ‘not applicable’ for those that did not include the outcome.   Include a footnote to identify endpoints where statistical testing was adjusted for multiple comparisons |
| List outcome 2 | As above | As above | As above |
| Add rows as necessary |  |  |  |

Abbreviations must be listed under the table in alphabetical order. For example, CI = confidence interval; OR = odds ratio

Source: For all tables reporting information from included studies, indicate data source including citation. Data should reflect the results reported in the clinical study report(s) whenever possible.

a Statistical testing for these endpoints was adjusted for multiple comparisons (e.g., hierarchal testing)

Sample Size and Power Calculation

Report assumptions regarding expected differences in treatment effect and variation (e.g., SD), as well as the rationale for selecting the parameters used in the calculation. Other potentially relevant information (e.g., whether loss to follow-up was accounted for, if there were power calculations for secondary endpoints) should be reported as applicable.

[Start typing report details here]

Statistical Testing

Detailed descriptions of statistical analysis methods are presented in Appendix 4.

* For noninferiority studies, state the methods used in the construction of the confidence interval, the noninferiority margin, and the justification for its selection, including clinical and statistical considerations. If a secondary analysis of superiority was performed, state if this was planned or performed post hoc.
* State whether there was any method used to adjust for multiple testing/control of type I error rate and describe the method and alpha levels used.
* For multiple primary endpoints or analysis of the individual components of the composite endpoints, it should be specified if the analysis approach accounted for multiple testing with an appropriate control of the Type I error rate.
* For multi-arm trials, describe which arms were compared and whether a statistical adjustment was made for multiple testing with an appropriate control of the Type I error rate.
* If there were interim analyses, please state how these were accounted for in the statistical testing plan.

[Start typing report details here]

Subgroup Analyses

Key details of subgroup analyses should be reported, including whether they are pre-specified and whether multiplicity was taken into account. If there were no relevant subgroup analyses, include a statement to that effect.

[Start typing report details here]

Analysis Populations

Define analysis sets (e.g., FAS, PP, safety set) for each study included in the systematic review using text or a summary table.

Table 4: Analysis Populations of Study 1 and Study 2

| Study | Population | Definition | Application |
| --- | --- | --- | --- |
| Study 1 | e.g., Full analysis set | Add definition as per study protocol | State how the population was used in the analyses (e.g., all efficacy analyses) |
| e.g., Safety analysis set | Add definition as per study protocol | State how the population was used in the analyses |
| Add rows as required | Add rows as required | Add rows as required |
| Study 2 | Add rows as required | Add rows as required | Add rows as required |

Abbreviations must be listed under the table in alphabetical order. For example, CI = confidence interval; OR = odds ratio

Source: For all tables reporting information from included studies, indicate data source including citation (and corresponding table number[s] in the clinical study report where applicable). Data should reflect the results reported in the clinical study report(s) whenever possible.

Patient Population

Baseline Characteristics

Summarize relevant baseline demographic and clinical characteristics of the population for each study using a table (example table below). Indicate in the table which analysis set the baseline characteristics have been summarized for (e.g., FAS set)

* for discrete data report as n (%)
* for continuous data report the mean (SD); where continuous data are skewed also report the median (IQR or range)
* only present baseline characteristics and results for treatment groups that reflect the dosage(s) that will be recommended in the product monograph for the drug under review.

More than one table can be created if all studies do not fit in a single table. Additional text is not necessary for this section.

Table 5: Summary of Baseline Characteristics of Study 1 and Study 2

| Characteristic | Study 1 | | Study 2 | |
| --- | --- | --- | --- | --- |
| Treatment 1  (N = ) | Treatment 2  (N = ) | Treatment 1  (N = ) | Treatment 2  (N = ) |
| Study variable (units), measurement (% or variability of measurement)  Example: Age (years), median (range) |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |

Abbreviations must be listed under the table in alphabetical order. For example, CI = confidence interval; OR = odds ratio

Source: For all tables reporting information from included studies, indicate data source including citation (and corresponding table number[s] in the clinical study report where applicable). Data should reflect the results reported in the clinical study report(s) whenever possible.

Patient Disposition

Please summarize the patient disposition for each included study using a table. Additional text is not necessary for this section.

Table 6: Patient Disposition for Study 1 and Study 2

| Patient disposition | Study 1 | | Study 2 | |
| --- | --- | --- | --- | --- |
| Treatment 1 | Treatment 2 | Treatment 1 | Treatment 2 |
| **Screened, N** |  |  |  |  |
| **Reason for screening failure, N (%)** |  |  |  |  |
| State reason 1 |  |  |  |  |
| State reason 2 |  |  |  |  |
| Add/modify rows as required |  |  |  |  |
| **Randomized, N (%)** |  |  |  |  |
| **Discontinued from study, N (%)** |  |  |  |  |
| **Reason for discontinuation, N (%)** |  |  |  |  |
| Adverse events |  |  |  |  |
| Lost to follow-up |  |  |  |  |
| Add/modify rows as required |  |  |  |  |
| **ITT, N** |  |  |  |  |
| **FAS, N** |  |  |  |  |
| **PP, N** |  |  |  |  |
| **Safety, N** |  |  |  |  |
| **Add/remove rows as required** |  |  |  |  |

Abbreviations must be listed under the table in alphabetical order. For example, CI = confidence interval; OR = odds ratio

Source: For all tables reporting information from included studies, indicate data source including citation (and corresponding table number[s] in the clinical study report where applicable). Data should reflect the results reported in the clinical study report(s) whenever possible.

Exposure to Interventions

Study treatments

Summarize exposure using a table (example provided below) or paragraph text. Include information on adherence to treatment where relevant. Additional text is not necessary for this section.

Table 7: Exposure to Study Treatment for Study 1 and Study 2 (Sample Table)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Exposure | Study 1 | | Study 2 | |
| Treatment 1  (N = ) | Treatment 2  (N = ) | Treatment 1  (N = ) | Treatment 2  (N = ) |
| Total, patient-weeks or patient-years |  |  |  |  |
| Duration, mean (SD) |  |  |  |  |
| Duration, median (IQR or range) |  |  |  |  |
| Adherence, % |  |  |  |  |

Abbreviations must be listed under the table in alphabetical order. For example, CI = confidence interval; OR = odds ratio

Source: For all tables reporting information from included studies, indicate data source including citation (and corresponding table number[s] in the clinical study report where applicable). Data should reflect the results reported in the clinical study report(s) whenever possible.

Concomitant Medications and Co-Interventions

Briefly describe concomitant medications or cointerventions required during the study. If concomitant medication doses were lowered or treatment stopped, describe the schedule as applicable (e.g., tapering corticosteroids). Additional information (i.e., a summary table) can be included in Appendix 5.

[Start typing report details here]

Subsequent Treatment (if applicable)

Please describe any protocols for managing cross-over to other treatment groups (e.g., placebo to active treatment) or the provision of additional therapies or interventions during the treatment period or follow-up phase (e.g., additional anticancer medication or surgery upon documented disease progression). If applicable, a table summarizing the overall use of subsequent treatments and breakdown of specific treatments and/or interventions can be included in Appendix 5.

[Start typing report details here]

Results

Efficacy

Summary of Key Efficacy Outcomes

Provide a table similar to the example below summarizing key efficacy outcomes for the studies (indicate the analysis population in the title or headings or by using footnotes). Results for other included efficacy outcomes can be reported in the text or in additional tables. For any included figures, indicate the data source including citation (and corresponding figure number in the clinical study report where applicable). Figures may be placed in Appendix 6 (Additional Efficacy Results).

For time-to-event analyses overall frequency of events, number of patients censored, and time of follow-up (e.g., total days of follow-up, median or mean time of follow-up) for each stratum should be presented descriptively.

In addition to any relevant relative differences in effects (e.g., odds ratio, relative risk, hazard ratio), absolute differences in effects with confidence intervals should be presented in the data tables when possible, even if they are not part of the statistical analysis plan. These include mean difference for continuous outcomes, risk difference for dichotomous outcomes, and difference in survival probability at relevant time points for outcomes from time-to-event analyses. Absolute effects are essential for the review team’s appraisal of the clinical importance of the reported effects.

Table 8: Summary of Key Efficacy Results

| Variable | Study 1  Treatment 1  N = | Study 1  Treatment 2  N = | Study 2  Treatment 1  N = | Study 2  Treatment 2  N = |
| --- | --- | --- | --- | --- |
| Outcome 1 (units) | | | | |
| Number of patients contributing to the analysis |  |  |  |  |
| Baseline, mean (SD) |  |  |  |  |
| Change from baseline, mean (95% CI or SE) |  |  |  |  |
| Treatment group difference versus control (95% CI) |  |  |  |  |
| P value |  |  |  |  |
| Outcome 2 | | | | |
| n (%) |  |  |  |  |
| OR/RR (95% CI) |  |  |  |  |
| RD (95% CI) |  |  |  |  |
| P value |  |  |  |  |
| Outcome 3 | | | | |
| Events, n (%) |  |  |  |  |
| Censored, n (%) |  |  |  |  |
| Censoring reason 1 (add rows as needed), n (%) |  |  |  |  |
| Overall survival (months), median (95% CI) |  |  |  |  |
| HR (95% CI) |  |  |  |  |
| P value |  |  |  |  |
| Survival probability (%) at X months (95% CI) |  |  |  |  |
| Difference in survival probability (%) (95% CI) |  |  |  |  |
| Outcome 4 | | | | |
| As above |  |  |  |  |

Abbreviations must be listed under the table in alphabetical order. For example, CI = confidence interval; FAS = full analysis set; HT = hazard ratio; RD = risk difference; RR = relative risk; OR = odds ratio.

Source: For all tables reporting information from included studies, indicate data source including citation (and corresponding table number[s] in the clinical study report where applicable). Data should reflect the results reported in the clinical study report(s) whenever possible.

Add footnotes (accompanied by superscript letters in the table) for the following:

* To specify (as applicable) model, adjustment factors, analysis population, and handling of missing data.
* To denote P values that have been adjusted for multiple testing.

Efficacy End Point 1

The text of the efficacy section should convey the main messages of the data that are presented in tables or graphs — please be concise and clear in the text.

Please avoid the following when presenting results:

* + Interpreting the difference between two groups as being statistically significant based upon nonoverlapping confidence intervals for the individual within groups change (rather than a statistical test of the difference between groups).
  + Focusing on the clinical relevance of within groups changes rather than the clinical relevance of the difference in the between groups change when there is a comparison group.

Summarize the results from key sensitivity analyses and subgroup analyses under each of the outcomes. Subgroup analyses should reflect those that are specified within the systematic review protocol. If results for pre-specified subgroups for key end points notably differ from the main results, they may be reported in Appendix 6 (Additional Efficacy Results).

If data within the report are derived from different cut-off dates, please ensure that the dates are clearly specified when reporting the results.

[Start typing report details here]

Efficacy End Point 2

Please use a separate subheading for each endpoint.

[Start typing report details here]

Efficacy End Point 3

Please use a separate subheading for each endpoint.

[Start typing report details here]

Harms

In this space the sponsor must summarize key adverse event data for the drug under review. Do not report results of statistical analyses for safety outcomes.

Overview of Safety

Detailed results for harms are presented in Appendix 7.

Briefly summarize here (for treatment-emergent adverse events):

* Overall occurrence of AEs, SAEs, and deaths
* The most common AEs and SAEs
* If applicable, additional key takeaways

[Start typing report details here]

Withdrawals Due to Adverse Events

Summarize withdrawals due to adverse events and adverse events that resulted in an interruption of the study treatment(s). Clearly identify if the adverse events resulted in discontinuation of the study treatment and/or complete discontinuation from the study.

[Start typing report details here]

Adverse Events of Special Interest

Provide a brief summary of any adverse events of special interest. If relevant, provide a summary of how these events were managed in the clinical trial. Delete this section if not applicable.

[Start typing report details here]

Sponsor’s Summary of the Indirect Evidence

In this section of the template the sponsor must summarize all indirect treatment comparisons that have been included in the application (i.e., to support comparative efficacy or safety and the assumptions in the economic evaluation). If the application does not include 1 or more indirect comparisons, the sponsor should explain why an indirect comparison is not relevant for the review (i.e., do not delete this section if there are no data available).

Description of Indirect Treatment Comparison(s)

In this section the sponsor should summarize the methods and results of all indirect comparisons included in the application.

Objectives

Provide the objective of the indirect comparison focusing on the evidence gap it is aiming to address (e.g., absence of direct evidence for relevant comparators [specify comparators that are being addressed]).

[Start typing report details here]

Study Selection and Review Methods

Details on study selection criteria and review methods are presented in Appendix 8.

Briefly state the scope (population, comparators, and outcomes) of the ITC(s).

[Start typing report details here]

Indirect Comparison Analysis Methods

Details on analysis methods for the indirect comparison(s) are presented in Appendix 8.

Briefly state the type of analysis performed and the justification for selecting the approach.

[Start typing report details here]

Results

Summary of Included Studies

Describe the trials included in the systematic review, and the indirect comparison analysis (including number of trials and patients).

Highlight potential sources of heterogeneity (e.g., in the patients, interventions, outcomes, study design or follow up time). The table below is an example of what may be used to provide a description of important differences across trials for key characteristics. The list of characteristics are examples; please add rows as appropriate (and delete a row only if the characteristic is irrelevant). No evidence of effect modification may be added as a comment, if appropriate.

Please ensure that features that could lead to differences in treatment effect modifiers are addressed (e.g., patients recruited to studies of A versus B have less advanced disease than those in A versus C). Consider: Dosage, treatment duration, route of administration, supportive care as well as information on treatment titration, induction or maintenance treatment. Highlight the differences between trials, if any.

[Start typing report details here]

Table 9: Assessment of Homogeneity (Sample Table)

| Characteristics | Description and handling of potential effect modifiers |
| --- | --- |
| **Disease severity** | Comment on similarities and differences across studies and note if there were any relevant adjustments or sensitivity analyses. Indicate when the information required to compare across studies is missing (i.e., not reported). |
| **Treatment history** | As above |
| **Trial eligibility criteria** | As above |
| **Dosing of comparators** | As above |
| **Placebo response** | As above |
| **Definitions of endpoints** | As above |
| **Timing of endpoint evaluation** | As above |
| **Withdrawal frequency** | As above |
| **Clinical trial setting** | As above |
| **Study design** | As above |

Abbreviations must be listed under the table in alphabetical order. For example, CI = confidence interval; OR = odds ratio

Source: Indicate data source including citations.

**For an anchored MAIC**: Additional results that are not efficacy or harms results (i.e., unadjusted and adjusted patient characteristics) can be reported in a new appendix (i.e., insert a new Appendix 9; Summary of Sponsor’s Economic Evaluation becomes Appendix 10).

Efficacy

Provide a summary of the indirect comparison results for efficacy outcomes, including point estimates and 95% confidence intervals and/or credible intervals (as appropriate for the method of analysis) for pairwise comparisons of interest to the review. Present a summary of the results for relevant comparators, focussing on comparisons with relevant comparators not assessed in the systematic review evidence in Section 2.

* + Describe the results relating to how well the selected model(s) fits the data
  + Provide a brief summary of the results of subgroup analyses and/or meta-regression, if relevant. If relevant/necessary, present the results of one or more sensitivity analyses. It is often sufficient to state that the results of all sensitivity analysis were consistent with the base case (if the methods used for the sensitivity analyses are appropriate and described adequately).

The tables below provide example formats that may be used to summarize NMA results.

[Start typing report details here]

Table 10: ITC Sample Data Table for Continuous Outcomes (e.g., Summary of NMA Results for Efficacy Results, [Treatment] Versus Comparators)

| Comparator | Outcome 1 (units) at time point, mean difference (95% CrI) | Outcome 2 (units) at time point, mean difference (95% CrI) |
| --- | --- | --- |
| [Comparator 1] |  |  |
| [Comparator 2] |  |  |
| [Comparator 3] |  |  |

Abbreviations must be listed under the table in alphabetical order. For example, CrI =, credible interval; OR = odds ratio; NA = not applicable; NMA = network meta-analysis.

Source: Indicate data source including citation.

Table 11: ITC Sample Data Table for Dichotomous Outcomes (e.g., Summary of NMA Results for Efficacy Results, [Treatment] Versus Comparators)

| Comparator | Outcome 1 (units) at time point, OR (95% CrI) | Outcome 2 (units) at time point, OR (95% CrI) |
| --- | --- | --- |
| [Comparator 1] |  |  |
| [Comparator 2] |  |  |
| [Comparator 3] |  |  |

Abbreviations must be listed under the table in alphabetical order. For example, CrI =, credible interval; OR = odds ratio; NA = not applicable; NMA = network meta-analysis.

Source: Indicate data source including citation.

Efficacy End Point 1

Please use a separate subheading for each endpoint.

[Start typing report details here]

Efficacy End Point 2

Please use a separate subheading for each endpoint.

[Start typing report details here]

Efficacy End Point 3

Please use a separate subheading for each endpoint.

[Start typing report details here]

Harms

Provide a summary of the indirect comparison results for harms outcomes using the guidance provided above. If no harms endpoints were evaluated in the indirect comparison, please state this within this section (i.e., do not delete the section heading in the absence of comparative harms data).

[Start typing report details here]

Pharmacoeconomic Evaluation

This section is reserved for the CDA-AMC review of the sponsor’s pharmacoeconomic evaluation and is to be left blank by the sponsor.

Appendix 1: Key Characteristics of Treatment Options

All relevant comparators should be included in the table (even if the sponsor has received formal notification from CDA-AMC that 1 or more relevant comparators may be excluded from the systematic review). This table may be completed at the drug class level for some rows if there are multiple relevant comparators within the same drug class.

Relevant comparators are treatments that meet at least 1 of the following:

* + treatments currently reimbursed by at least 1 participating drug plan for the indication under review,
  + reimbursed treatments that are currently used off-label in Canadian practice, or
  + treatments that have previously received a recommendation in favour of reimbursement from CDA-AMC for the indication under review.

The review will typically focus on drug comparators that are reimbursed by public drug plans. Though not typical, in some circumstances nondrug comparators (e.g., transfusion, plasmapheresis) may also be included as comparators. Comparators not approved by Health Canada for the indication under review may also be considered relevant if they are the standard of care and their use is reimbursed by drug programs for the indication of interest. Comparators available through Health Canada’s Special Access Program for the indication under review may also be considered.

Table 12: Key Characteristics of Drug 1, Drug 2, etc.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Drug | Mechanism of action | Relevant indication(s) | Route of administration and dosage | Serious adverse effects or safety issues |
| Drug under review | Briefly state the mechanism of action | State indication under review | State recommended regimen per the product monograph | State serious warnings and precautions and notable contraindications from the product monograph. |
| Comparator 1 | As above | State relevant indication(s) approved by Health Canada. If used off-label, note “not approved for the indication under review”. | State dosage regimen recommended in the product monograph. If the indication has not been approved by Health Canada, please state the dosage regimen that is used in clinical practice and provide supporting referencing. | As above |
| Comparator 2 | As above | As above | As above | As above |
| Add rows as needed |  |  |  |  |

Source: Indicate data sources (i.e., product monographs) including citation.

a Clinical evidence has not been submitted for this comparator versus the drug under review. (Delete this footnote if not applicable)

If relevant for the drug under review, include a brief paragraph on recommended dosage adjustments for notable subpopulations in the product monograph, as well as any confirmed or anticipated statements in the product monograph regarding restricting the prescribing and/or administration of the drug to certain health care professionals.

Appendix 2: Systematic Review Procol and Literature Search Strategy

Review Protocol

Guidance for defining the population, intervention, comparators, outcomes, and study designs (PICOS) for the review protocol are provided below.

**Population**

The population will be defined as the full population identified in the approved/proposed Health Canada indication for which the sponsor is submitting (unless otherwise decided upon in consultation with CDA-AMC). While a sponsor’s reimbursement request may be specific to a subgroup or subpopulation of patients within the Health Canada indication, the population defined in the systematic review protocol will typically not be limited according to the reimbursement request. Subpopulations identified in the sponsor’s reimbursement request should be pre-specified in the protocol as a subgroup(s) of interest and results reported where available. Other relevant subgroups that are likely to be of interest to clinicians, drug plans, patients, and those included in the sponsor’s pharmacoeconomic submission should also be included in the protocol. These should be based on clinically important prognostic factors or modifiers of treatment effects.

**Intervention**

The intervention will be specified as the drug, formulation, and route of administration under review, and within the Health Canada approved dosage range. For studies that include multiple intervention arms with differing dosages, only those arms with dosages within the Health Canada approved range should be included in the systematic review. For pre-NOC submissions, where there is uncertainty about which doses will be approved by Health Canada, all dosage arms may be included.

**Comparator(s)**

All relevant comparators should be included unless the sponsor has discussed with CDA-AMC and received formal notification that one or more relevant comparators may be excluded. Relevant comparators include the following:

* + treatments currently reimbursed by at least 1 participating drug plan for the indication under review,
  + reimbursed treatments that are currently used off-label in Canadian practice, or
  + treatments that have previously received a recommendation in favour of reimbursement from CDA-AMC for the indication under review.

The review will typically focus on drug comparators that are reimbursed by public drug plans. Though not typical, in some circumstances nondrug comparators (e.g., transfusion, plasmapheresis) may also be included as comparators. Comparators not approved by Health Canada for the indication under review may also be considered relevant if they are the standard of care and their use is reimbursed by drug programs for the indication of interest. Comparators available through Health Canada’s Special Access Program for the indication under review may also be considered.

**Outcomes**

Outcomes should reflect those studied in the clinical development program for the drug review. This includes, but is not limited to:

* + all primary and key secondary endpoints in the clinical studies
  + health-related quality of life end points (irrespective of classification within the hierarchy of endpoints in the trial protocol)
  + other outcomes (including notable harms) that are critically important

**Study design**

In addition to the clinical trials submitted as pivotal studies to Health Canada, other phase 3 or 4 randomized controlled studies should be included in the systematic review. Consideration may be given to including other study designs in the protocol-selected studies on a case-by-case basis (e.g., if the pivotal trials are not Phase 3 randomized controlled trials).

Table 13: Inclusion Criteria for the Systematic Review

| Criteria | Description |
| --- | --- |
| Population | Specify population(s)  Subgroups:  List all relevant subgroups |
| Intervention | Drug, dose and route of administration, as applicable |
| Comparator | List comparators |
| Outcomes | **Efficacy outcomes:**  **Harms outcomes:**  AEs, SAEs, WDAEs, Mortality, add AESI |
| Study designs | Pivotal trials, phase 3 or 4 RCTs |

Abbreviations must be listed under the table in alphabetical order. For example, CI = confidence interval; OR = odds ratio

Literature Search and Study Selection

Literature Search Methodology

Literature searches must be developed following internationally accepted standards for systematic reviews. Examples of search guidance documents include:

* + European Network for Health Technology Assessment. [Process of information retrieval for systematic reviews and health technology assessments on clinical effectiveness](https://eunethta.eu/wp-content/uploads/2020/01/EUnetHTA_Guideline_Information_Retrieval_v2-0.pdf). Methodological Guidelines. Diemen (The Netherlands): EUnetHTA; 2019.
  + Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I, Noel-Storr A, Rader T, Shokraneh F, Thomas J, Wieland LS. [Chapter 4: Searching for and selecting studies](https://training.cochrane.org/handbook/current/chapter-04). In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021.

**Searching bibliographic databases**

MEDLINE and Embase must be searched as these are the major biomedical bibliographic databases that concern pharmaceuticals. Other databases may be included as relevant, for example: (Cochrane, CENTRAL, PsycINFO, CINAHL, Scopus, Web of Science). Use a sensitive database search strategy, employing:

* + controlled vocabulary (e.g., MeSH, Emtree terms, etc.)
  + text words (e.g., synonyms)
  + registry numbers
  + chemical drug names
  + trade drug names
  + generic drug names

Follow field codes and syntax correctly for each database (platform) searched, for example:

* + Ovid MEDLINE: (trade drug name or generic drug name or developmental drug name).ti,ab,kf,ot,hw,rn,nm.
  + Ovid Embase: Generic drug name/ or (trade drug name or generic drug name or developmental drug name).ti,ab,kf,ot,rn,dq.

In some instances, it may be necessary to apply a search concept for the indication/condition. Similar principles to search strategy design apply: controlled vocabulary (e.g., MeSH, Emtree terms, etc.); text words (e.g., synonyms).

If applying study design filters to the search, consult available search filters as outlined by these resources:

* + [CDA-AMC’s database search filters](http://searchfilters.cadth.ca/)
  + Glanville J, Lefebvre C, Manson P, Robinson S and Shaw N, editors. [ISSG Search Filter Resource](https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/home). York (UK): The InterTASC Information Specialists' Sub-Group; 2006 [updated 9 Nov. 2021; cited 9 Nov. 2021].

Peer review is strongly recommended, using the [*PRESS Peer Review of Electronic Search Strategies*](https://www.cda-amc.ca/press-peer-review-electronic-search-strategies)

**Searching clinical trial registries**

Multiple trial registries should be searched and reported on in the literature search appendix section, including:

* + ClinicalTrials.gov: Produced by the U.S. National Library of Medicine
  + WHO ICTRP: International Clinical Trials Registry Platform, produced by the World Health Organization
  + Health Canada’s Clinical Trials Database
  + EU Clinical Trials Register: European Union Clinical Trials Register, produced by the European Union

**Reporting of the literature search**

Systematic literature searches must be reproducible. The search strategy should be reported in the literature search appendix section. Elements presented should follow the [*PRISMA-S extension checklist*](http://www.prisma-statement.org/Extensions/Searching).

**Example of Reporting Clinical Literature Search Methods**

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the [*PRESS Peer Review of Electronic Search Strategies* checklist](https://www.cda-amc.ca/press-peer-review-electronic-search-strategies). Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946‒ ) via Ovid; Embase (1974‒ ) via Ovid; Cochrane Central Register of Controlled Trials (CCTR) via Ovid; and Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCO. All Ovid searches were run simultaneously as a multi-file search. Duplicates were removed using Ovid deduplication for multi-file searches, followed by manual deduplication in Endnote. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine’s MeSH (Medical Subject Headings), and keywords. The main search concepts were [intervention] and [indication/population]. Clinical trials registries were searched: the US National Institutes of Health’s clinicaltrials.gov, World Health Organization’s International Clinical Trials Registry Platform (ICTRP) search portal, Health Canada’s Clinical Trials Database, and the European Union Clinical Trials Register.

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Refer to Appendix 1 for the detailed search strategies. The initial search was completed on MONTH DAY, YEAR.

**Example of Literature Search Strategy Reporting**

**Databases**

* Ovid – MEDLINE All (1946-present)
* Ovid – Embase (1974-present)
* Ovid – Cochrane Central Register of Controlled Trials (CCTR)
* EBSCO – CINAHL
* Scopus
* Web of Science

Note: Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid. Other duplicates were removed using bibliographic management software.

**Date of searches**: [Provide search date. If dates vary, provide search date for each database]

**Search filters applied**: Systematic reviews; meta-analyses; network meta-analyses; health technology assessments; guidelines; overview of reviews; randomized controlled trials; controlled clinical trials; qualitative studies; observational studies; economic evaluations; costs and cost analysis studies, and quality of life studies.

**Limits**

* Publication date limit: none
* Language limit: none
* Humans

**Database Search Strategies**

Provide search strategies

**Clinical Trials Registries**

*ClinicalTrials.gov*

Produced by the U.S. National Library of Medicine. Targeted search used to capture registered clinical trials. [Search terms – List search terms]

*WHO ICTRP*

International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials. [Search terms – List search terms]

*Health Canada’s Clinical Trials Database*

Produced by Health Canada. Targeted search used to capture registered clinical trials. [Search terms – List search terms]

*EU Clinical Trials Register*

European Union Clinical Trials Register, produced by the European Union. Targeted search used to capture registered clinical trials. [Search terms – List search terms]

Study Selection

Figure [Number]: PRISMA Flow Diagram

In this space the sponsor should provide a PRISMA diagram depicting the flow of information through the different phases of the systematic review. For additional information, including examples and templates for PRISMA diagrams, please refer to: <http://prisma-statement.org/prismastatement/flowdiagram.aspx>

Appendix : List of Excluded Studies

Table 14: Excluded Studies

| Reference | Reason for Exclusion |
| --- | --- |
| Add reference | When identifying the reason for exclusion, please use a similar format as the following examples:   * + - * Study design       * Intervention (if the intervention in the study does not meet that identified in the systematic review protocol, for example, different dose, formulation, etc.)       * Comparator       * Study population       * Duplicate study |
| As above | As above |
| Add rows as necessary |  |

Appendix 4: Methods of the Studies in the Systematic Review

Additional Eligibility Criteria

* Delete this section if not applicable.

Description of Outcome Measures

Describe each of the outcome measures reported in the systematic review and provide information on minimal important differences (MID) using text or a summary table. Ensure that a reference list and copies of articles addressing the validity of outcome measures (including surrogate outcomes) are provided in the application.

* + Briefly describe the relevant efficacy outcomes for the included studies (i.e., all outcomes included in the protocol) in sufficient detail for the reader to be able to understand and interpret the outcome data (definitions and measurement).
  + Descriptions of scale measures should include a brief overview of the scale including:
    - Construct(s) or domain(s) measured
    - Structure of the scale (i.e., is there one single overall score or individual domain scores or both)
    - Range of scores.
    - Direction of the scale (e.g., do higher scores indicate greater impairment? Better HRQoL?)
    - Whether or not an estimated MID was identified (for overall and individual domain scores). Please clearly state the source of the MID (e.g., reference to publication, regulatory opinion, clinical expert opinion) and the method used for estimation (e.g., anchor-based) and whether the MID refers to within-group or between group differences (or both). Identify the population in which the MID was estimated (e.g., patients with severe COPD; general population estimate). If multiple estimates of the MID are identified, the full range of MIDs should be reported. If no MID has been identified, this should be explicitly stated.
  + For surrogate outcomes, summarize the clinical evidence underlying or justifying the use of a surrogate as well as the evidence for the validation of the surrogate.
  + Describe how outcomes are adjudicated (centrally adjudicated, or investigator adjudicated, or both).
  + Responder definitions, cut points and rationale for cut point selection should be described and referenced.

Statistical Analysis

Provide a brief description of the statistical analysis for each outcome reported in the systematic review.

* + The covariates and/or baseline values that were included in the statistical models should be specified. It should be stated that the analysis was unadjusted if no covariates and/or baseline values were included in the analysis.
  + Data imputation and other missing data methods (e.g., LOCF, statistical models such as MMRM, non-responder imputation) and the associated assumptions should be reported.
  + How intercurrent events were handled. Intercurrent events are events of interest that occur after a treatment has been initiated that may impact the interpretation of the end point (e.g., the event modified the treatment effect, such as in the use of rescue medications or other concomitant treatments, or has implications for adherence to the treatment regimen, including premature treatment discontinuation).
  + The main sensitivity analyses, if any, and the rationale for the analysis (e.g., alternate analyses that use different imputation techniques) should be described.
  + Repetition within the description and the information provided in the summary table(s) should be avoided where possible. If methods for the secondary outcomes are similar to those for the primary outcome, simply state this and highlight any differences.
  + Items should be summarized in a table where appropriate (refer to example below). Paragraph text is not needed if all details are in the table.

Table 15: Statistical Analysis of Efficacy End Points

| End point | Statistical model | Adjustment factors | Handling of missing data | Sensitivity analyses |
| --- | --- | --- | --- | --- |
| Study 1 | | | | | |
| List endpoint 1 | e.g., MMRM | Please list the factors which were adjusted (e.g., baseline values, age, etc.) | Please state how missing data were addressed | Please list all sensitivity analyses (e.g., multiple imputation) |
| Add rows as required | As above | As above | As above | As above |
| Study 2 | | | | | |
| As above | As above | As above |  | As above |

Abbreviations must be listed under the table in alphabetical order. For example, CI = confidence interval; OR = odds ratio

Source: For all tables reporting information from included studies, indicate data source including citation.

Appendix 5: Exposure to Other Treatments for Studies in the Systematic Review

If there is no relevant information to present in this appendix, include a statement to that effect.

Table 16: Sample Table for Subsequent Treatment

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Exposure | Study 1 | | Study 2 | |
| Treatment 1  (N = ) | Treatment 2  (N = ) | Treatment 1  (N = ) | Treatment 2  (N = ) |
| Received subsequent therapy, n (%) |  |  |  |  |
| State therapy, n (%) |  |  |  |  |
| State therapy, n (%) |  |  |  |  |
| Add rows as required |  |  |  |  |

Abbreviations must be listed under the table in alphabetical order. For example, CI = confidence interval; OR = odds ratio

Source: For all tables reporting information from included studies, indicate data source including citation (and corresponding table number[s] in the clinical study report where applicable). Data should reflect the results reported in the clinical study report(s) whenever possible.

Appendix 6: Additional Efficacy Results for the Studies in the Systematic Review

This section may be used for efficacy results from the systematic review that are presented in figures (e.g., measurements over time). If there is no relevant information to present in this appendix, include a statement to that effect.

Appendix 7: Detailed Harms Results for the Studies in the Systematic Review

Provide an overall summary table of key harms data (example shown below). Please note the following:

* + Thresholds for common events may vary across development programs. Please ensure that the threshold for inclusion in the table is clearly reported (e.g., ≥ 5% of patients). The threshold should generally align with what has been included in the draft or final product monograph.
  + Please report individual events at the preferred term level.

Table 17: Summary of Key Harms Results

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Adverse events | Study 1 | | Study 2 | |
| Treatment 1  (N = ) | Treatment 2  (N = ) | Treatment 1  (N = ) | Treatment 2  (N = ) |
| Patients with at least 1 adverse event, n (%) | | | | |
| Most common events |  |  |  |  |
| State AE |  |  |  |  |
| Add rows as required |  |  |  |  |
|  |  |  |  |  |
| Patients with at least 1 serious adverse event, n (%) | | | | |
| Most common events |  |  |  |  |
| State SAE |  |  |  |  |
| Add rows as required |  |  |  |  |
|  |  |  |  |  |
| Patients who stopped treatment due to adverse events, n (%) | | | | |
| State AE |  |  |  |  |
| Add rows as required |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |
| Deaths, n (%) | | | | |
| Add description of events or list of common causes of death |  |  |  |  |
| Add rows as required |  |  |  |  |
|  |  |  |  |  |
| Adverse events of special interest, n (%) | | | | |
| Specify events based on those listed in the safety evaluation plan |  |  |  |  |
| Add rows as required |  |  |  |  |

Abbreviations must be listed under the table in alphabetical order. For example, CI = confidence interval; OR = odds ratio

Source: For all tables reporting information from included studies, indicate data source including citation (and corresponding table number[s] in the clinical study report where applicable). Data should reflect the results reported in the clinical study report(s) whenever possible.

Appendix 8: Detailed Methods for the Indirect Treatment Comparison

If no indirect treatment comparisons are included in the application include a statement to that effect.

Study Selection and Review Methods

Summarize each included ITC in text or one or more tables similar to the one below. Do not repeat information in the text that is presented in the tables.

* + Describe the methods used to conduct the systematic review and to select studies for inclusion in the indirect comparison.
  + Describe the methods used to extract data (e.g., duplicate extraction, or single reviewer extraction with check).
  + Describe how the authors assessed study quality, and how this information was used (e.g., to exclude certain studies).

Table 18: Study Selection Criteria and Methods for Indirect Comparisons

| Item | Description |
| --- | --- |
| Criteria | |
| **Population** | Briefly state the population(s) of interest for the indirect comparison |
| **Intervention** | List intervention including dosing information |
| **Comparator** | List comparators including dosing information |
| **Outcome** | List outcomes including time points |
| **Study designs** | Briefly describe the study designs included in the indirect comparison |
| **Publication characteristics** | Specify inclusion of published and/or unpublished studies |
| **Exclusion criteria** | Briefly describe the exclusion criteria used for selecting studies |
| Methods | |
| **Databases searched** | Briefly list databases included in the literature search |
| **Selection process** | Briefly describe the review methods (e.g., articles screened independently by 2 researchers) |
| **Data extraction process** | Briefly describe the review methods |
| **Quality assessment** | Briefly describe the methods used to assess the quality of studies (e.g., appraisal tools) |

Abbreviations must be listed under the table in alphabetical order. For example, CI = confidence interval; OR = odds ratio

Source: Indicate data source including citation.

Indirect Comparison Analysis Methods

* Briefly describe the following (where applicable), either in text or table format:
  + The statistical model
  + The feasibility assessment and how well the underlying assumptions of the methods were supported.
  + How model fit was assessed. If multiple models were run, describe how the model selected as the primary analysis was chosen. If only 1 model was used, please provide the reason(s).
  + Please note the following for Bayesian models:
    - Describe prior distributions for modeling parameters.
    - Describe justification for use of informative priors, and whether sensitivity analyses were done to assess the impact of the priors selected.
    - Convergence diagnostics, burn-in period, number of iterations and number of chains should also be described.
  + Please note the following for an anchored matching-adjusting indirect comparison (MAIC):
    - Describe the justification for conducting a MAIC and for the comparator chosen.
    - Describe sources of heterogeneity that were identified between trials in the comparison. Specify whether any methods were used to account for heterogeneity prior to the weighting process including whether any patients were excluded from the trial.
    - Describe any processes used to identify baseline characteristics that are potential effect modifiers and, for unanchored comparisons, prognostic factors.
    - Describe what characteristics were identified in the variable selection process, and which of these variables were ultimately adjusted for in the weighting process. Specify the justification for excluding any variable identified in the variable selection process.
    - Describe the method used to calculate the weight of individual patient data.
    - Describe the approach used to estimate the parameters of the model.
    - Describe if effective sample size measures and any other weight assessments were reported.
  + How homogeneity was assessed. Please address clinical, methodological, and statistical heterogeneity as relevant.
  + Steps taken to address potential sources of heterogeneity (e.g., excluding studies, doses, or timepoints from the analysis) or meta-regression analyses.
  + Rationale for sensitivity analysis with description of methods used.
  + Rationale for subgroup analysis with description of methods used.
  + How consistency between direct and indirect comparisons were evaluated if relevant (e.g., inconsistency modelling, simple direct versus indirect, or if it was not possible to assess consistency due to the lack of a closed loops)
  + Methods used to conduct standard pairwise meta-analysis (if conducted).
  + For NMAs, how nodes in the network were constructed, how different doses, different routes of administration, different drugs within the same class, and comparators were handled (separate nodes or pooled analysis).
  + Methods used for rescaling or conversion of results to a common scale, in cases where studies reported different scales or measures. Discuss appropriateness of any methods for reconstructing individual patient data from summary data.
  + Which set of analysis results have been used where studies have conducted multiple analyses of a given endpoint (e.g., multiple approaches to dealing with missing data).
  + The outcomes were analyzed and the rationale for excluding any of those that were pre-planned for analyses.
* The table below provides an example of how the key data elements may be described using a table format. The sample table is focussed on describing Bayesian NMA methods and likely needs modification for other approaches. Add or delete rows as appropriate. As methods may vary for different types of outcomes (continuous, dichotomous) or by network or population, additional columns may be added as needed.

Table 19: Indirect Comparison Analysis Methods

| Methods | Description |
| --- | --- |
| **Analysis methods** | Briefly describe the methods |
| **Priors** | As above |
| **Assessment of Model fit** | As above |
| **Assessment of Consistency** | As above |
| **Assessment of Convergence** | As above |
| **Outcomes** | As above |
| **Follow-up timepoints** | As above |
| **Construction of nodes** | As above |
| **Sensitivity analyses** | As above |
| **Subgroup analysis** | As above |
| **Methods for pairwise meta-analysis** | As above |

Abbreviations must be listed under the table in alphabetical order. For example, CI = confidence interval; OR = odds ratio

Source: Indicate data source including citation.

Appendix 9: Summary of Sponsor’s Economic Evaluation

Please note that this appendix is to be completed in addition to the Technical Report and Excel workbook and other items required per the [Procedures for Reimbursement Reviews](https://www.cda-amc.ca/sites/default/files/Drug_Review_Process/Drug_Reimbursement_Review_Procedures.pdf) (refer to the Cost-Minimization Analysis section within the Pharmacoeconomic Submission section).

Table 20: Key Components of the Sponsor’s Economic Evaluation

| Component | Description |
| --- | --- |
| Treatment information | |
| **Drug under review** | Generic name (Brand). Note if drug under review is used in addition to other treatment(s). Summarize the recommended dosage as per the product monograph |
| **Submitted price of Drug Under Review** | Generic name: Price per lowest dispensable unit (e.g., per tablet, vial, prefilled syringe) to 4 decimal places as per Pricing and Distribution document for each form/strength |
| **[Annual or per-course costs] of [Drug Under Review]** | State the assumed/calculated treatment cost (annual or per course [e.g., 28-day course]) including full regimen cost if drug under review is part of a regimen  If any modifying assumptions are made (e.g., weight-based dose, relative dose intensity, different costs in first course vs. subsequent course) describe these here |
| Model information | |
| **Type of economic evaluation** | Cost-minimization analysis |
| **Treatment assessed** | State the drug or regimen under review |
| **Included comparator(s)** | Provide an alphabetical list of comparators by generic name. Note if comparator is used in addition to other treatment(s).  All treatments listed in Appendix 1 (i.e., treatments included in the Key Characteristics table) are to be included in the economic evaluation.  If one of the comparators is best supportive care, standard of care, etc., define what it is comprised of. |
| **Perspective** | State the perspective, i.e., Publicly funded health care payer |
| **Time horizon** | State the time horizon, e.g., # years |
| **Modelled population(s)** | Briefly describe the modelled population |
| **Characteristics of modelled population** | State the mean starting age of patients in the population, along with any other relevant characteristics (e.g., sex, weight, BMI, BSA) |
| **Model health states** | If applicable, describe the model health states and how patients transition between states. If there are no modelled health states, state “Not applicable”. |
| Data sources | |
| **Comparative efficacy** | Describe the sources, inputs, and assumptions made that support the assertion that the drug under review has similar clinical effects (i.e., has at least equivalent effectiveness and/or efficacy, and is equivalently or less harmful) |
| **Costs** | Briefly describe the included costs, along with sources, inputs, and any assumptions |
| Summary of the submitted results | |
| **Base case** | State the base case results |
| **Scenario analysis** | Present influential scenario analyses as required |

Abbreviations must be listed under the table in alphabetical order.

References

References must be provided in this section and should adhere to standard citation practices for publication, as per the following examples:

1. Murray CJL. Maximizing antiretroviral therapy in developing countries: the dual challenge of efficiency and quality [published online December 1, 2014]. *JAMA*. doi:10.1001/jama.2014.16376
2. Centers for Medicare & Medicaid Services. CMS proposals to implement certain disclosure provisions of the Affordable Care Act. <http://www.cms.gov/apps/media/press/factsheet.asp?Counter=4221>. Accessed January 30, 2012.
3. McPhee SJ, Winker MA, Rabow MW, Pantilat SZ, Markowitz AJ, eds. *Care at the Close of Life: Evidence and Experience*. New York, NY: McGraw Hill Medical; 2011.