

COMMON DRUG REVIEW CLINICAL REVIEW REPORT TEMPLATE

Annotated with Reviewer Guidelines

Note: This annotated template provides guidance on the content to consider for each section of the clinical report for CDR clinical reviewers and clinical experts. The blank template is a guide for the format of the report and should be used in the preparation of the report.

Drug Product Generic name (Brand name)	
Manufacturer (Distributor if applicable)	

TABLE OF CONTENTS

LIST OF ABBREVIATIONS	ii
EXECUTIVE SUMMARY	1
SYSTEMATIC REVIEW OF CLINICAL TRIALS	
I. REVIEW PROTOCOL	3
II. REVIEW RESULTS	6
A. Findings from the Literature	6
B. Summary of Evidence	7
1. Summary of Trial Outcomes	7
2. Individual Trial Summaries	8
3. Summary of Trial Characteristics.....	9
4. Outcomes	10
III. DISCUSSION	11
IV. CONCLUSIONS	12
SUPPLEMENTAL ISSUES	
I. ADDITIONAL HARMS INFORMATION.....	15
II. COMPARATOR INFORMATION.....	16
III. VALIDITY OF OUTCOME MEASURES.....	17
APPENDIX I: BACKGROUND INFORMATION ON THE CONDITION	18
APPENDIX II: REVIEW METHODS	19
APPENDIX III: LIST OF INCLUDED AND EXCLUDED STUDIES	20
APPENDIX IV: DETAILED TRIAL CHARACTERISTICS	21
REFERENCES	22
REVIEWER WORKSHEETS	23

LIST OF ABBREVIATIONS

All abbreviations used in the report should be listed here in alphabetical order. When appropriate, a brief description of the item should also be included (i.e. for an abbreviation of a measurement scale, indicate what the scale measures, etc.)

AE	Adverse event
CI	Confidence interval
DB	Double blind
ITT	Intention-to-treat population
MC	Multi-center
MD	Mean difference
PL	Placebo
PM	Product monograph
PSUR	Periodic safety update report
RCT	Randomized controlled trial
RR	Relative risk
SAE	Serious adverse event
SD	Standard deviation
WD	Withdrawal
WDAE	Withdrawal due to adverse event

EXECUTIVE SUMMARY (2 pages)

(Point form or short paragraphs as appropriate)

Drug

Include the name of the drug, the drug class and a very brief description of the drug mechanism if relevant. Also indicate approved indications and dosing. Note if NOC/c and include a brief summary of the conditions.

Objective

To evaluate the effect of drug A on patient outcomes compared to standard therapies and placebo in patients with disease/condition B.

Included Studies

Indicate the number, overall quality, duration, size and patient populations of included studies, etc. Highlight comparators used in the studies. Indicate the hypothesis tested in the studies (e.g., non-inferiority, equivalence, superiority).

Results

Briefly state the results in point form or short paragraphs as appropriate. Summarize the information as briefly as possible. Include the results of relevant statistical analysis (e.g., for dichotomous outcomes include odds ratios, relative risk, number needed to treat/harm with 95% confidence intervals; for continuous outcomes include mean difference with 95% confidence intervals). Ensure that results are expressed in terms of the hypothesis tested, e.g., for non-inferiority trials state that treatment A is or is not inferior to treatment B, for equivalency trials state if results are equivalent (not similar to).

Discussion

Interpret the results (benefits and harms) in short paragraphs. Include efficacy and harms as subheadings; add other subheadings as appropriate. Include information from supplemental issues sections as appropriate.

Interpretation of results encompasses issues related to both bias and outcomes.

- Discuss how study bias may have affected interpretation of results (i.e. did study design, study size, study duration, notable exclusion criteria, number of withdrawals, etc. affect interpretation of results)
- Discuss results in terms of relevant issues (issues related to validity and measurement of outcomes, surrogate outcomes, composite outcomes, conflicting data and possible reasons for this, clinical relevance of outcome measures and size of effect, missing information, overall bias and confidence in evidence for the outcome, rationale for choice of non-inferiority/equivalency/superiority margins, rationale for choice of analysis population etc.)

Issues for Consideration

Indicate manufacturer's proposed listing criteria as well as other issues relevant to the review in point form or short paragraphs as appropriate.

Conclusions

These conclusions should be identical to the Conclusions listed in the Systematic Review of Clinical Trials.

Pharmacoeconomic Summary

Include a summary statement (or short paragraph) describing the type of analysis, cost of drug and overall results of the pharmacoeconomic evaluation. The pharmacoeconomic reviewer will provide this information.

SYSTEMATIC REVIEW OF CLINICAL TRIALS

I. REVIEW PROTOCOL

A. Objective(s)

State the objective(s) that is/are most relevant to the drug plans for evaluation of the drug.

Example:

To evaluate the effect of drug A on patient outcomes (listed in the table below) compared to standard therapies and placebo in patients with disease/condition B.

The objective should specify a study population (patients for which drug is indicated), an intervention (new drug under review), a comparator(s) (most suitable existing therapy) and outcomes (reference the table below). Details concerning each of these components should be contained in the table below.

The reviewer may consider patient subgroups that may benefit more or less from the drug. If appropriate, a secondary objective relating specifically to these patients could be included (include under 'Patient Population' in table below).

Note: In many situations the manufacturer specifies the patient subgroup population(s) in which the new drug is most suitable for use.

B. Methods

See Appendix II for reviewer information and review methods (including literature search, systematic review and data analysis methods).

Studies were chosen for inclusion in the review based on the criteria listed in the table below.

Table 1. Selection Criteria

Clinical Trial Design	Patient Population	Interventions	Appropriate Comparators*	Outcomes [†]

*Standard therapies available in Canada (may include drug or non-drug interventions)

[†]Outcomes relevant to the drug under review as determined by CDR reviewers and clinical expert

Guidelines for Completing Selection Criteria Table

(Use point form to complete table; define abbreviations under the table)

- *Clinical Trial Design*
Specify the types of studies to be included in the review. Double-blind, randomized controlled trials are ideal; however, non-blinded, randomized controlled trials are also acceptable.
- *Patient Population*
Specify characteristics of patients that are required for a study to be included in the review. Studies should include appropriate patients that reflect the population found under normal clinical conditions. If appropriate, criteria may specify distinct patient populations or severity of disease, etc.
- *Interventions*
Specify the interventions with the review drug that are required for a study to be included in the review (i.e. review drug as monotherapy or as combination therapy).
- *Appropriate Comparators (Standard Therapies Available in Canada)*
Indicate all appropriate comparators for each approved indication of the drug. Ideally, the comparator should be a standard therapy (head-to-head trial); however, placebo comparisons may also be relevant.
- *Types of Outcome Measures*
List the outcomes that will be considered in the review. Outcomes should be categorized as primary or secondary when possible. Alternatively, outcomes may be listed without categorization, as appropriate to the particular review. Any methods of measurement of outcomes that are likely to be unfamiliar should be explained in an additional appendix.

Emphasis should be placed on clinically relevant and valid outcomes of highest importance for the health of patients with the disease state (primary outcomes; examples for cardiovascular disease include cardiovascular-related mortality such as fatal MI or stroke and cardiovascular-related morbidity such as non-fatal MI or stroke).

Outcomes with less clinical relevance or less clear validation of clinical relevance for patients should be included, if appropriate, but should receive less emphasis (secondary outcomes; examples for cardiovascular disease include blood pressure or cholesterol level). When appropriate, the strength of evidence for extrapolation of these outcomes to clinically relevant patient outcomes should be discussed in the Discussion or in Supplemental Issues.

Harms (including withdrawals due to adverse events, serious adverse events, and adverse events) should also be considered as outcomes. Note that the choice of 'Harms' as terminology is based on CONSORT (ref: *Annals Intern Med* 2004; 141: 781-788).

Withdrawals due to adverse events and number of patients requiring dose reductions due to drug intolerance should be considered as outcomes reflecting patient tolerance to the drug.

Please note the following definitions related to these terms as described in the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2A (see <http://www.ich.org/cache/compo/276-254-1.html>).

Adverse Event

“Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.” An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Serious Adverse Event

“Any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.”

Adverse Drug Reaction

The definition differs slightly depending on the status of the drug product (i.e. pre-approval vs. marketed products).

“In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: *all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions*. The phrase “response to a medicinal product” means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out”

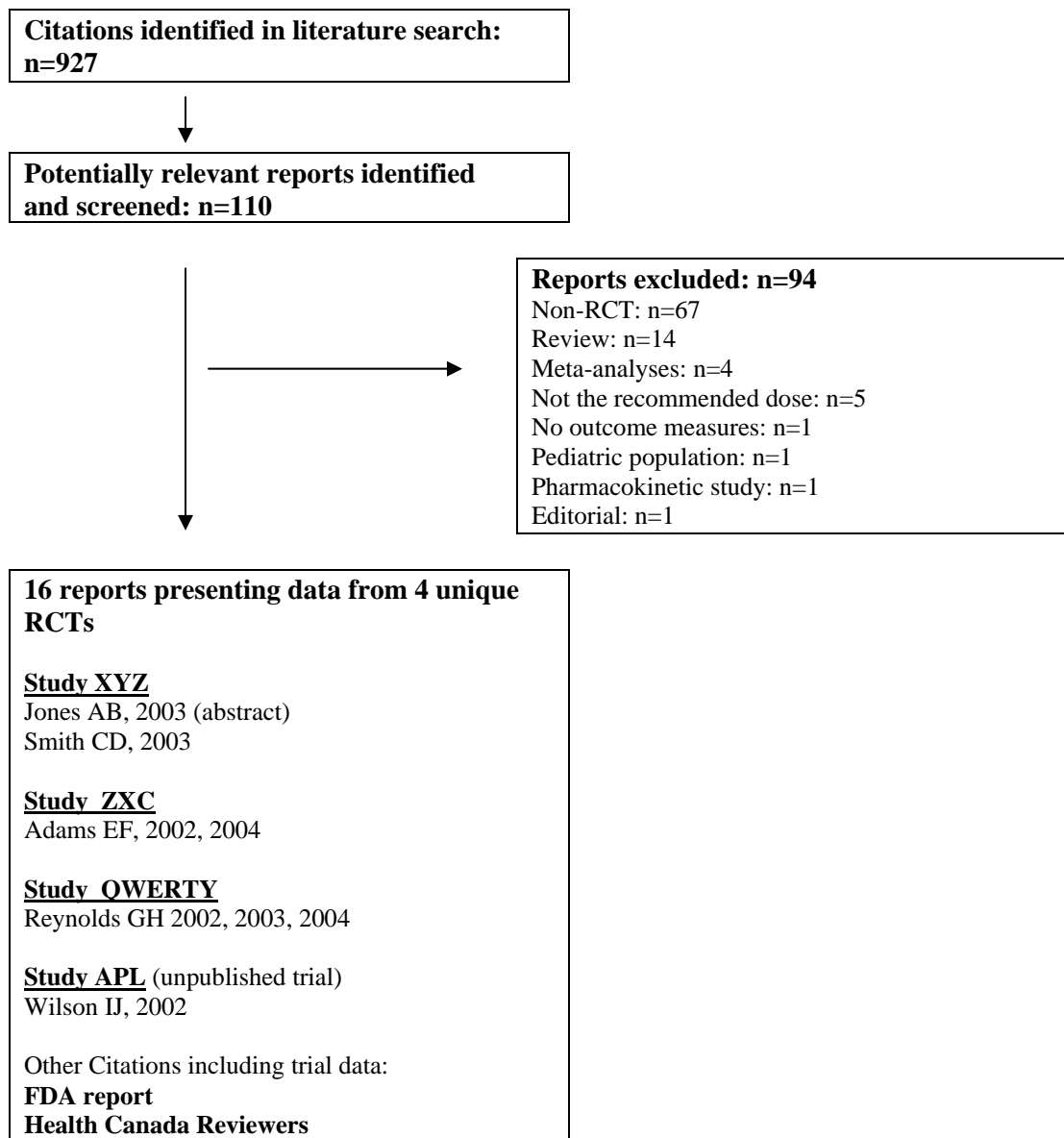
“Regarding marketed medicinal products, a well-accepted definition of an adverse drug reaction in the post-marketing setting is found in WHO Technical Report 498 [1972] and reads as follows: *a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function*”

The old term "side effect" has been used in various ways in the past, usually to describe negative (unfavourable) effects, but also positive (favourable) effects. It is recommended that this term no longer be used and particularly should not be regarded as synonymous with adverse event or adverse reaction.

II. REVIEW RESULTS

A. Findings from the Literature

Figure 1 – QUOROM Flowchart Detailing Flow of Studies (See Appendix III for a listing of Included/Excluded studies)



Group studies by important trial characteristics or patient subgroups where relevant (use headings). Identify any included studies that are unpublished in the final box (use brackets). Identify studies by author name where possible and provide references. Note that referencing using Reference Manager is not possible within text boxes. Use an ‘outside border’ or table to create the box.

Notes:

Indicate any important additional information not included in the flowchart in text form below Figure 1 under Notes. Use small font (Times New Roman 9 point) to allow for inclusion on a single page.

B. Summary of Evidence

1. Summary of Trial Outcomes

Study Reference	Study Details	Outcome 1	Outcome 2	Outcome 3	Outcome 4	Outcome 5	Outcome 6	Outcome 7
Trial A (published/ unpublished)	Type of trial Intervention Duration N=							
Trial B (published/ unpublished)	Type of trial Intervention Duration N=							

NR=Not reported (outcome results were not present in published or unpublished documents available to CDR); NP=Not provided (outcome results were requested from the manufacturer and not provided); NI=Not included (outcome was not included in the trial)

Guidelines for Completing Summary of Trial Outcomes Table

- Do not include references in this table.
- Include all important outcomes in this table. Try to include results for each outcome where possible (if appropriate, could consider including results for most important outcomes only)
- Consider providing additional trial information in the ‘Study Details’ column of the table (i.e. specific comparators, important details concerning study population such as severity of disease, etc.)
- If there were predefined criteria for non-inferiority, equivalency or superiority indicate whether the criteria were fulfilled in section below the table.
- Consider listing outcomes in rows and studies in columns if information is more clearly presented in this manner (i.e. when there are many outcomes; see sample alternate format table in Blank Clinical Review Report Template).

2. Individual Trial Summaries

a. Name of Trial

Trial Design/ Reference	Inclusion Criteria	Interventions	Outcomes*

*Outcomes included in the trial.

Assessment of Study Bias: Highlight key issues.

Guidelines for Completing Individual Trial Tables

- Complete one table for each included study; tables for each study must not exceed one page
- Table title: Use unreferenced study name/acronym where possible (unreferenced author name and year can be used if there is no study name/acronym)
- Trial Design/Reference: list and reference all data sources; include type of study, published or unpublished, abstract or full manuscript, manufacturer funding, etc.
- Inclusion Criteria: list only the most relevant inclusion criteria in the table; specific exclusion criteria and baseline characteristics can be listed in the notes section below the table if important to include for a particular review
- Interventions: indicate drugs (including background treatments), dose, frequency, duration of treatment, duration of follow-up, number of subjects in each intervention group etc.
- Outcomes: list the outcomes assessed in the study and the methods of assessment if appropriate; results should not generally be included in these tables but may be included at the reviewer’s discretion
- For complicated trial designs, consider including a schematic of the trial to present the designs and randomization of subjects at each timepoint etc. The schematic could be included in the Summary of Trial Characteristics section if it is too large.

Notes:

Guidelines for Completing Notes Section

- Highlight important facts about the study in the notes section below the table (examples: study is the only one in a specific patient population, a key baseline characteristic, a key exclusion criteria, etc.).
- When relevant, indicate whether the trial was designed to assess non-inferiority, equivalency or superiority and include the predefined criteria.

3. Summary of Trial Characteristics (maximum of 2 pages)

Note: Compare and contrast trial information under the headings below. Be brief when completing this section. Highlight key findings only and avoid duplicating data already presented in the Individual Trial Summary tables. Sections may be deleted if there is only one included trial and the information is captured in the Individual Trial Summary table. Detailed trial characteristics and tables may be presented in Appendix IV.

a. Trial Characteristics

Indicate the number of trials meeting inclusion criteria for review. Indicate the design of the trials (include details such as types of trials, number and location of study sites, blinding, funding source, non-inferiority, equivalency, superiority, etc. as relevant).

b. Population Characteristics

Indicate the total number of patients randomized in all the trials (also indicate total number of trials) and the range of sample sizes across trials. Compare and contrast inclusion/exclusion criteria. If relevant, indicate the range of mean ages and range of % males or females across the studies and highlight any major differences. Indicate values or range of values for any other important baseline characteristics and highlight any major differences. Note that discussion of implications related to differences in population characteristics should be handled in the Discussion section.

c. Intervention Characteristics

Indicate the comparators and the number of trials involving each comparator. Indicate any important details involving dosing, administration and/or frequency of administration, etc and highlight any differences between the trials. Indicate the duration of treatment for the trials. Note that discussion of implications related to differences in intervention characteristics should be handled in the Discussion section.

d. Outcome Characteristics

Reference the Summary of Trial Outcomes Table here. Indicate important definitions for outcomes as appropriate and highlight any differences between studies. If more appropriate, definitions may be included with presentation of the detailed outcome. Note that implications related to differences in outcome characteristics should be handled in the Discussion section.

Note that in some cases a reference to the Summary of Trial Outcomes table will be all that is required for this section.

4. Outcomes

If relevant, start this section with a paragraph describing the rationale for any CDR data analysis that was performed (i.e. rationale for pooling trials and associated details, rationale for alternate or additional data analysis performed by CDR). Indicate other details of CDR data analysis in Appendix II.

Outcome A (Sample table; reviewers to create tables appropriate to the data for each review)

No.	Study Reference	Study Details	Outcome A n/N(%) or mean [SD] units		Statistics	
			Drug	Comparator	p-value [†]	MD[95% CI] [‡]
1						
2						
1,2	CDR meta-analysis*					

CI=confidence interval; MD=mean difference; SD=standard deviation

* Explanation of reasons for meta-analysis and reasons for inclusion/exclusion of studies in the meta-analysis

† Reported in the study; ‡ Calculated by CDR

Guidelines for Completing Outcome Tables

- A table should be created for each outcome as appropriate. Note that tables may not be required in the following instances: reports with only one or two included trials, data not conducive to incorporation into a table, or data is limited. Results should be explained in text whether there are tables or not.
- **Format of tables is flexible – use format that best suits the data for a particular outcome** but try to have consistent format per report (i.e. consistently list studies downward in vertical column or across in horizontal row for all tables, studies presented in the same order from one table to the next).
- The 'No.' column is only useful when CDR meta-analysis is performed.
- Study Details: provide type, duration and N-value of trial; alternative or additional details may be presented if they provide a more useful (but brief) reference for readers. Reviewers could consider combining Study Reference and Study Details under one heading, if applicable.
- Include statistics in these tables (reported in trial and/or calculated by CDR; make sure to clearly identify when CDR performs the analysis) Note: CDR will perform additional statistical analyses only as appropriate on a case-by-case basis.
 - For dichotomous outcome data, consider calculating odds ratio and/or absolute and relative risk reduction/risk increase as appropriate. **Whenever possible, calculate number needed to treat (NNT)/number needed to harm (NNH) with 95% confidence intervals.**
 - For continuous outcome data, consider calculating mean difference with 95% confidence intervals as appropriate.
 - Consider performing meta-analysis if appropriate and if the results illuminate issues which are not addressed by data from individual trials. Clearly indicate decision rules for meta-analysis if performed, including reasons for including/excluding particular studies. Forest plots are preferred to display results when they offer additional relevant information and are typically presented in an appendix.

General Guidelines for Results Reporting

- When reporting results for dichotomous data, include numerator, denominator and percentage.
- When reporting results for continuous data, include measure of dispersion (standard deviation or standard error, etc.).
- Clearly indicate where data included is available from abstracts only.

III. DISCUSSION

A. Interpretation of Results

General

- Give a brief overview of included studies with a discussion of any issues related to differences between trials that may affect interpretation of results. Discuss implications related to overall bias and to differences in trial design, population, intervention and outcome characteristics that were indicated in the ‘Trial Characteristics’ section of the review (i.e. did study design, study size, study duration, characteristics of included population, notable exclusion criteria, number of withdrawals/dropouts, etc. affect interpretation of results).
- Indicate any important unavailable data (example: no trials including relevant comparators or an important outcome).

Efficacy (Reviewers to add other subheadings as appropriate to the review)

- Discuss results in terms of relevant issues. Some examples include issues related to bias, validity and measurement of outcomes, clinical relevance of outcome measures, clinical relevance of size of effect, conflicting data and possible reasons for this, missing information, etc. Also discuss any statistical issues that affect interpretation of the data (including handling of missing data, subgroup analysis, the rationale for the non-inferiority/equivalency/superiority margin and the statistical and clinical considerations in determining the margin, etc.).
- Use results from the Supplemental issues section of the review in the Discussion to provide context. Reference Supplemental Issues section when appropriate.

Harms (Include ‘Harms’ as a subheading in the Interpretation of Results section)

- Highlight precautions and warnings from product monograph and relate this to trial data if possible.
- Discuss SAE and AE results from included clinical trials here or above. Also discuss WDAE as an indication of patient tolerability to drug here or above.
- Use results of from ‘Additional Harms’ in Supplemental Issues to support or expand overall view of harms associated with drug as assessed through clinical trials. When discussing non-RCT data, indicate when denominators are unknown and implications of this. Clearly identify whether data under discussion is from included clinical trials or from non RCT data.

- If no head-to-head trials with relevant comparators were found, consider including a qualitative comparison of potential harms of review drug vs. comparators.

B. Comparison with Other Literature (As appropriate)

Discuss and compare results of any drug class reviews or key meta-analyses published in the literature or submitted by the manufacturer to the results of CDR review (could include a more detailed summary in the Supplemental issues section, if required).

C. Other (As appropriate)

Some examples are:

- Pharmacology
- Pharmacokinetics

D. Issues for Consideration (Point form or short paragraphs as appropriate)

Include any unresolved questions and/or concerns related to the review. Some examples are:

- Listing criteria proposed by manufacturer (and data available to support the requested criteria)
- Any issues identified from the Product Monograph but not discussed elsewhere
- FDA approved or not and brief details
- Ongoing clinical trials for other indications
- Strengths and weaknesses of the CDR review
- Pharmacology or pharmacokinetic issues
- Key gaps in evidence

IV. CONCLUSIONS

Summarize the overall conclusions as concisely as possible in a short paragraph. It is not necessary to reiterate results for each outcome; however, major outcomes that relate to the overall conclusions should be included. The following information may be useful to consider as part of the conclusions:

- Overall outcomes
 - Benefits and harms relative to comparators
 - Absolute benefits and harms
 - Validity of outcomes
 - Clinical relevance of size of effect
- Strength of evidence
 - Number and size of supporting or conflicting clinical trials
 - Quality of clinical trials (limitations in quality of clinical trials that may affect interpretation of trial results)
- Gaps in evidence/questions remaining
 - Important subpopulations where no studies have been identified
 - Lack of studies using an important comparator

Language Guidelines

Avoid use of vague language

- Avoid use of ‘*there is no evidence*’ (does this mean that no trials were found or that no differences were demonstrated in available trials?)
- Avoid use of ‘*there is insufficient evidence*’ (in quantity? in quality?)
- Avoid use of ‘*there is evidence*’ (is the evidence of good quality or poor quality? is it based on 1 small trial or 5 large trials?)
- For non-inferiority trials avoid using a double negative (ie. not non-inferior).

SUPPLEMENTAL ISSUES

Issues considered in this section were provided as supporting information. The information has not been systematically reviewed.

Issues related to the Submission that are likely to be relevant for CEDAC members in making the recommendation but that are not addressed in detail in the systematic review should be listed here.

Information Services (IS) will perform a literature search to identify available evidence on the issue. The literature search for these issues will usually be quite broad and will not be restricted to information specifically concerning the drug under review.

For each supplemental issue

- Describe the reason for including the issue (under the heading “Objective”).
- Present the information retrieved and provide a critical appraisal and synthesis of the findings (under the heading “Findings”).
- Summarize key, overall findings and present them in a box at the end of each section (under the heading “Summary”).

I. ADDITIONAL HARMS INFORMATION

A. Objective

B. Findings

Present the information and provide a critical appraisal and synthesis of the findings (this information is not systematically reviewed).

C. Summary

Summarize key, overall findings and present them in this box.

II. COMPARATOR INFORMATION (if applicable)

A. Objective

B. Findings

Present the information and provide a critical appraisal and synthesis of the findings (this information is not systematically reviewed).

C. Summary

Summarize key, overall findings and present them in this box.

III. VALIDITY OF OUTCOME MEASURES (if applicable)

A. Objective

B. Findings

Present the information and provide a critical appraisal and synthesis of the findings (this information is not systematically reviewed).

C. Summary

Summarize key, overall findings and present them in this box.

APPENDIX I: BACKGROUND INFORMATION ON THE CONDITION

This section was prepared by a clinical expert. It has not been systematically reviewed.

A. Disease Prevalence/Incidence (Length: ½ page)

This section should include a description of the disease prevalence/incidence in the Canadian population. The reviewers may assess the information provided by the manufacturer or include information based on the sources provided by the CDR information specialist.

B. Standards of Therapy or Accepted Clinical Practice (Length 1-2 pages)

This section is not intended to be a full systematic review; however, it should be evidence-based and thoroughly referenced.

Describe all currently accepted therapeutic approaches (including pharmacological and non-pharmacological interventions) used to manage the medical conditions for which the drug under review has an approved indication. Include any limitations of the current treatment, if appropriate (e.g., effectiveness, adverse effects, administration).

Identify the expected place in therapy of the new drug by indication (e.g., replacement for current therapy, use with current therapy, and/or only for non-responders, and/or only for those with contraindications or intolerance to current therapy, etc).

It is acceptable to use clinical practice guidelines as references for this section. Evidence-based guidelines should be used whenever possible and levels of evidence should be indicated.

C. Identifying Appropriate Patients to Receive Drug (Length ½ page)

Indicate whether clinicians will be able to easily determine which patients would be appropriate candidates for treatment with the new drug.

Limitations of clinical trials that may impact on decision making, missing information that makes determination of appropriate candidates difficult and any ethical, social or patient implications associated with the use of the drug should be considered.

D. Potential for Off-Label Use

Based on the literature, approved indications in other countries or the pharmacology of the drug, identify other potential uses of the drug that may impact on its utilization. If possible, indicate how well established such off-label uses are.

APPENDIX II: REVIEW METHODS

A. Reviewer Information

- Expertise of this review team included [list expertise of team members].
- Systematic Review and Executive Summary were prepared by two CDR clinical reviewers in consultation with an external clinical expert specializing in [indicate speciality].
- Additional Harms Information (Supplemental Issues) was prepared by [XXX].
- [Other Issue] (Supplemental Issues) was prepared by [XXX].
- Background Information on the Condition (Appendix I) was prepared by an external clinical expert specializing in [indicate speciality].

B. Literature Search Methods

- The literature search is performed by an internal CDR information specialist using a peer-reviewed search strategy.
- A summary write-up of the search strategy is given to the reviewer to be inserted in the report.
- The summary write-up lists all sources searched, including the electronic databases, trial registries and sources which are used to identify grey literature such as posters, abstracts and unpublished data. No language limitations are used in the searches.
- Note: If the reviewer hand searches reference lists and / or key journals, consults other references or requests information from the manufacturer, the reviewer should indicate this information here.

C. Systematic Review Methods

- The review protocol was developed jointly by the two CDR clinical reviewers and the external clinical expert in consultation with the internal and external pharmacoeconomic reviewers. Members of the Canadian Expert Drug Advisory Committee (CEDAC) also provided input and comments.
- Each CDR clinical reviewer independently selected studies for inclusion according to the predetermined selection criteria. All articles considered potentially relevant by at least one reviewer were acquired from library sources. Reviewers independently made the final selection of studies to be included in the review and differences were resolved through discussion. A list of included studies and a list of excluded studies with reasons for exclusion are provided in Appendix III.
- Critical appraisal of the studies and assessment of study bias were performed independently by the two CDR clinical reviewers.
- The systematic review portion of the report was written by one CDR clinical reviewer with input from the second CDR clinical reviewer and the external clinical expert.

D. Data Analysis Methods

- Provide details on any additional analyses of the data performed by CDR. Also include details on software programs used by CDR to perform additional data analyses.
- If no additional analyses were performed, indicate “no additional analyses of the data were performed by CDR for this review”.

APPENDIX III: LIST OF INCLUDED AND EXCLUDED STUDIES

A. Included Studies

List the studies selected for inclusion in the review. Include the main study name or number and all related articles.

B. Excluded Studies

List the excluded studies with reasons for exclusion. The list of excluded studies includes those studies excluded after initial selection of all potentially relevant studies.

APPENDIX IV: DETAILED TRIAL CHARACTERISTICS (as required)

REFERENCES:

The Reference Manager Identification Number will be indicated at the top right hand corner of each paper provided to reviewers. References for all sections of the report should be indicated by placing the Reference Manager Identification Number and the last name of the first author in brackets in the appropriate spot in the report. The information specialist and/or internal reviewer will insert the references into the report using the Reference Manager database. External reviewers will be requested to verify the references once they have been inserted into the report.

REVIEWER WORKSHEETS

A. Data Extraction Worksheet

Note: These worksheets may be used by reviewers to extract and tabulate data and assessment comments related to the clinical trials selected for inclusion in the review. Completed worksheets will not be appended to the review since the relevant content is summarized in the report.

Note: The data extraction worksheet can be modified by reviewers for review of specific drugs.

Study title		
Reference		
Methods		
Study design*		
Study duration		
Diagnosis		
Eligibility criteria (inclusion and exclusion criteria)		
Country of origin		
Industry sponsorship	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	
	Intervention (_____)	Comparator (_____)
Dose and duration of treatment		
Sample size		
Baseline Characteristics Of Study Participants		
Outcomes	Intervention (_____)	Comparator (_____)

* For non-inferiority design consider: validity of control group selected, how the non-inferiority margin was selected, have both per protocol and ITT analyses been provided, how the sample size was estimated.

B. Assessment of Bias: SIGN 50

Section 1: Internal validity				
<i>In a well conducted RCT study.....</i>		In this study this criterion is:		
1.1	The study addresses an appropriate and clearly focused question.	Well covered Adequately addressed	Poorly addressed Not reported	Not applicable Not addressed
1.2	The assignment of subjects to treatment groups is randomised	Well covered Adequately addressed	Poorly addressed Not reported	Not applicable Not addressed
1.3	<i>An adequate concealment method is used</i>	Well covered Adequately addressed	Poorly addressed Not reported	Not applicable Not addressed
1.4	Subjects and investigators are kept 'blind' about treatment allocation	Well covered Adequately addressed	Poorly addressed Not reported	Not applicable Not addressed
1.5	The treatment and control groups are similar at the start of the trial	Well covered Adequately addressed	Poorly addressed Not reported	Not applicable Not addressed
1.6	The only difference between groups is the treatment under investigation	Well covered Adequately addressed	Poorly addressed Not reported	Not applicable Not addressed
1.7	All relevant outcomes are measured in a standard, valid and reliable way	Well covered Adequately addressed	Poorly addressed Not reported	Not applicable Not addressed
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?			
1.9	<i>All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis)</i>	Well covered Adequately addressed	Poorly addressed Not reported	Not applicable Not addressed
1.10	Where the study is carried out at more than one site, results are comparable for all sites	Well covered Adequately addressed	Poorly addressed Not reported	Not applicable Not addressed
SECTION 2: OVERALL ASSESSMENT OF THE STUDY				
2.1	<i>How well was the study done to minimise bias?</i> Code ++, +, or –			
SECTION 3: OTHERS				
3.1	How was this study funded? <i>List all sources of funding quoted in the article, whether Government, voluntary sector, or industry.</i>			

For checklist instruction, please see <http://www.sign.ac.uk/guidelines/fulltext/50/notes2.html>

Reference: Scottish Intercollegiate Guidelines Network (SIGN). Methodology checklist 2: randomized controlled trials. In: SIGN 50: A guideline developers' handbook. Edinburgh: SIGN, 2004
<http://www.sign.ac.uk/guidelines/fulltext/50/checklist2.html>

C. Assessment of Bias: Internal Validity of Randomized Controlled Trials

Study Title	
Reference	
Internal Validity Criteria	Details and Comments
<p>Selection Bias</p> <p>Was patient entry to the trial biased towards those more likely to have favourable results?</p> <p><input type="checkbox"/> Were eligibility requirements predefined and appropriate?</p> <p><input type="checkbox"/> Were baseline characteristics between groups comparable? If not, was adjustment done?</p> <p><input type="checkbox"/> Were recruitment processes specified and appropriate?</p> <p><input type="checkbox"/> Were all potentially eligible patients invited to participate or did investigator discretion affect those included (#screened vs. #enrolled)?</p> <p><input type="checkbox"/> Did authors account for all eligible patients who did not enter the trial?</p> <p><input type="checkbox"/> Were allocation strategies, appropriate (randomized and concealed)</p> <p>Appropriate: central randomization, numbered or coded containers, drugs prepared by pharmacy, serially numbered, opaque, sealed envelopes, etc.</p> <p>Inappropriate: alternation, reference to case record# or date of birth.</p>	
<p>Performance Bias</p> <p>Did the treatment given, including concomitant treatments, allow an unbiased estimate of the effect of the drug under investigation?</p> <p><input type="checkbox"/> Were concurrent therapies equivalent for both groups?</p> <p><input type="checkbox"/> Was the procedure for drug dosage adjustment handled similarly between groups (procedure for dose escalation/reduction and interruption)?</p> <p><input type="checkbox"/> Were the numbers of patients requiring dose adjustment and/or concomitant therapy similar between groups?</p> <p><input type="checkbox"/> Was patient compliance considered?</p> <p><input type="checkbox"/> To what degree was discretion available to physicians to move patients between study arms and use additional drugs?</p>	
<p>Detection Bias</p> <p>Was assessment of outcomes performed in a way that minimised bias? Were groups treated equally, apart from the experimental therapy?</p> <p><input type="checkbox"/> Were blinding procedures performed for patients, care providers and those assessing response?</p> <p><input type="checkbox"/> Was the method of double blinding appropriate (placebo and active treatment were identical forms) Note: an example of inappropriate blinding would be comparison of tablets vs. injection with no double dummy</p> <p><input type="checkbox"/> Could the side effect profile of one of the drugs have resulted in unblinding?</p>	
<p>Attrition Bias</p> <p>Was patient follow-up and handling of protocol deviations adequate to prevent bias</p> <p><input type="checkbox"/> Was intention-to-treat (ITT) analysis performed (Were all patients analyzed in the groups to which they were randomized)?</p> <p><input type="checkbox"/> Were all patients entered in the trial properly accounted for and attributed at its conclusion?</p> <p><input type="checkbox"/> Were the number and reasons for withdrawals and dropouts reported?</p> <p><input type="checkbox"/> Did the number of withdrawals and dropouts compromise randomization?</p>	

D. Assessment of Bias: External Validity of Randomized Controlled Trials

Study Title	
Reference	
External Validity Criteria	Details and Comments
Study Participants <input type="checkbox"/> Are patient characteristics (age, sex, disease severity, risk factors, co-morbidities) representative of patients that will be treated with the drug in the community? <input type="checkbox"/> Are patients we are concerned with so different that the results do not apply?	
Sample Size <input type="checkbox"/> Were power calculations performed at the design stage of the study? <input type="checkbox"/> Were the numbers recruited sufficient to detect the outcomes specified?	
Usual Care Setting <input type="checkbox"/> Does the study protocol and setting represent the usual care patients will receive in the community? <input type="checkbox"/> Was the level of care (primary to tertiary) and experience/specialization of the care providers representative of usual care? <input type="checkbox"/> Is the treatment feasible in our setting?	
Standard Treatment Regimens <input type="checkbox"/> Are drug dosage, timing, route of administration, duration of treatment, types of treatment and concomitant therapies appropriate? <input type="checkbox"/> Did dosing favour or hinder the intervention drug or comparator in any way (i.e. was dose of intervention or comparator drug suboptimal/ in excess of recommended dosing guidelines?)	
Standard Treatment Outcomes Measured <input type="checkbox"/> Were outcome measures appropriate? <input type="checkbox"/> Were outcomes measured appropriately (methods of measurement, appropriate time intervals)? <input type="checkbox"/> Were all clinically relevant outcomes reported? <input type="checkbox"/> What is the magnitude of the effect? Were both statistical and clinical significance considered?	
Length of Follow-Up <input type="checkbox"/> Defined? <input type="checkbox"/> Appropriate length? <input type="checkbox"/> Complete (80% is absolute minimum)? <input type="checkbox"/> Representative?	
Other <input type="checkbox"/> Were sub-group analyses specified <i>a priori</i> in the study protocol?	