Health Technology Assessment of Drugs With Companion Diagnostics at CADTH

Overview

Companion diagnostics are laboratory tests that provide information essential for the safe and effective use of particular therapeutic drugs. They work by detecting specific biomarkers that predict more favourable responses to certain drugs. In practice, companion diagnostics can identify patients who are likely to benefit or experience harms from particular therapies, or monitor clinical response to optimally guide treatment adjustments. The global market for companion diagnostics is growing, and the resulting implications for the Canadian health care system are significant, as there will be an increase in the number of drugs seeking public reimbursement for which there are companion diagnostics. Hence, there is an important need for pan-Canadian leadership in this area, particularly with respect to the health technology assessment of drugs with companion diagnostics.

In November 2016, CADTH invited stakeholder comments and feedback on a proposed process for the assessment of companion diagnostics through the CADTH Common Drug Review (CDR) and the CADTH pan-Canadian Oncology Drug Review (pCODR) programs. Feedback was received from three industry associations, four drug manufacturers, 10 government agencies, three patient advocacy groups, one hospital, one health care professional, and six members from the CADTH expert drug committees. In general, respondents acknowledged the need for a pan-Canadian process for the assessment of companion diagnostics, and were supportive of CADTH’s efforts to address this gap. Some respondents sought details of relevant changes to procedures, submission guidelines, and templates. There was some uncertainty around the impact on current drug review timelines and the impact on the current CDR/pCODR recommendations framework. All respondents supported CADTH’s continued engagement with patients, clinicians, and participating jurisdictions.

After careful consideration of all the feedback received, and in collaboration with the participating jurisdictions, CADTH has developed a process for the assessment of drugs with companion diagnostics that will apply to all submissions and resubmissions filed on or after October 11, 2017. Note that this will take effect for all CADTH Pre-submission Information Requirements Forms received as of June 13, 2017.

Of note, CADTH will not be conducting independent assessments of companion diagnostics, either as single or multiple (class) technologies; instead, CADTH’s overarching objective is to explicitly and consistently investigate factors relevant to any required biomarker testing that would inform the implementation of associated drugs under review through the CADTH CDR and pCODR programs.

Pre-Submission Application Phase

As part of CADTH’s advance notification procedure, manufacturers will be required to indicate whether anticipated submissions and resubmissions will include companion diagnostics. This will apply to applications of drugs that are eligible for review under the current CADTH CDR and pCODR programs, and for which biomarker testing is required, by Health Canada, to guide optimal patient selection.

The CADTH Pre-submission Information Requirements Form — CDR and pCODR Submissions and the CADTH Pre-submission Information Requirements Form — CDR and pCODR Resubmissions have been amended to reflect this additional information-gathering step. There will be no other pre-submission application phase changes.

Application Phase

Currently, CADTH requires manufacturers to file applications in accordance with the content, format, and organization stipulated in the corresponding submission guidelines for its CDR and pCODR programs. To consistently and explicitly evaluate drugs with companion diagnostics, CADTH will implement the following requirements:

- Provide a reference list and copies of articles that highlight the clinical utility of the companion diagnostics under review. In this context, clinical utility refers to evidence of improved health outcomes as a result of biomarker testing. If no references are provided, a statement will be required to confirm that a search has been undertaken but no references have been located.
- Explicitly incorporate relevant costs and consequences (e.g., rates of true- and false-positives, and true- and false-negatives) of any required biomarker testing into the pharmacoeconomic evaluations. The source(s) of information and any assumptions made regarding this aspect of the analysis will also be required.
- Disclose all prices for companion diagnostics included in the submissions in all applicable CDR and pCODR review reports and recommendations documents posted on the CADTH website.
- Provide budget impact analyses for drugs and companion diagnostics in combination and separately, as some jurisdictions fund the two health technologies through separate mechanisms.

Where necessary, the abovementioned changes will be reflected in the corresponding CDR and pCODR submission guidelines and procedures documents. There will be no other application or submission phase changes as a result of companion diagnostics.

**Review Phase**

Currently, through the CDR and pCODR programs, CADTH conducts thorough and objective evaluations of the clinical, economic, and patient evidence on drugs, and uses these evaluations to provide reimbursement recommendations and advice to its participating jurisdictions. In addition, input from front-line clinicians and implementation considerations at the jurisdictional level support CADTH Canadian Drug Expert Committee (CDEC) and the CADTH pCODR Expert Review Committee (pERC) recommendations.

To consistently and explicitly address companion diagnostics, the same factors as those that are currently considered will be investigated, albeit with the following changes:

**Clinical Evidence**

As part of the clinical systematic review conducted by CADTH reviewers, a subgroup of interest that will be pre-specified in the systematic review protocol will relate to the biomarker status of study participants. This will inform the clinical utility of companion diagnostics by highlighting evidence on the degree to which biomarker testing helps improve outcomes with the corresponding drug treatment.

CADTH reviewers will also review the manufacturer-provided reference list and copies of articles that highlight the clinical utility of the companion diagnostics under review, and may conduct a separate search of the clinical utility of the companion diagnostics, the results of which will be summarized in an appendix of the clinical review report.

**Economic Evidence**

As part of the appraisal of the manufacturer-provided pharmacoeconomic evaluation, CADTH reviewers will consider the costs and consequences of any required biomarker testing that manufacturers will incorporate into the submitted analyses.

**Patient Input**

Currently, through the CDR and pCODR programs, CADTH invites input from patient groups to ensure that issues important to patients are incorporated into the drug reviews in a formal and meaningful way. This is solicited using patient input templates, which are undergoing revisions based on a public consultation that was held in the fall of 2016.

To consistently and explicitly address companion diagnostics, the final templates will include a question that will ask patient groups of their expectations and/or experiences with any required biomarker testing for drugs under review. Patient groups will be asked to consider answering this question for eligible drugs that have companion diagnostics.

**Clinician Input**

As part of engaging expert clinicians throughout the review process, CADTH will engage additional experts in pathology and/or laboratory testing who would be able to comment on front-line clinical aspects of companion diagnostics; e.g., timing of biomarker testing in the clinical care pathway, the consistency of the testing protocol with current practice, and the availability of the testing. These experts will supplement the information provided by the usual clinician engagement processes of the CDR and pCODR programs.

**Jurisdictional Input**

As part of soliciting implementation considerations from its participating jurisdictions, CADTH will additionally seek insights into the enablers and barriers related to any required biomarker testing.

Where necessary, the abovementioned changes will be reflected in the corresponding CDR and pCODR submission guidelines and procedures documents. There will be no other review phase changes as a result of companion diagnostics.
**Recommendations Phase**

There will be no changes to the existing CDR/pCODR recommendations framework as a result of accepting submissions for drugs with companion diagnostics. The reimbursement recommendations for drugs with companion diagnostics would not refer to specific commercial laboratory tests. Instead, CDEC and pERC may decide to specify clinical criteria or conditions relevant to companion diagnostics as part of the drug recommendations. As an example, following is the pERC Final Recommendation for pembrolizumab for the treatment of patients with metastatic non-small cell lung carcinoma whose tumours express PD-L1 (as determined by a validated test) and who have disease progression on or after cytotoxic chemotherapy:

“pERC recommends reimbursement of pembrolizumab (Keytruda) conditional on the cost-effectiveness being improved to an acceptable level. Funding should be for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumours express PD-L1 (as determined by a validated test) and who have disease progression on or after cytotoxic chemotherapy... Funding should be for patients with a Tumour Proportion Score (TPS) of PD-L1 ≥ 1% and who have good performance status...”

Of note, in the abovementioned case, the pERC Final Recommendation was aligned with the funding request submitted by the manufacturer/applicant.

**References**

