



pan-Canadian Oncology Drug Review Final Economic Guidance Report

Siltuximab (Sylvant) for Multicentric Castleman's Disease

June 22, 2015

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

The economic analysis submitted to pCODR by Janssen Inc comprised of a cost-effectiveness and a cost-utility analysis that compared Siltuximab plus best supportive care (BSC) to placebo plus BSC for patients with Multicentric Castleman's disease (MCD) who are Human Immunodeficiency Virus-negative (HIV) and Human Herpes Virus-8 (HHV-8)-negative. Siltuximab is administered intravenously at a dose of 11mg/kg every three weeks. Best supportive care includes a basket of alternative symptom controlling treatments administered both orally and intravenously. The evidence for tumour response of Siltuximab+BSC vs placebo+BSC originated from the MCD2001[1] study, a randomized, placebo controlled, double blind, phase III clinical trial. Survival probabilities varied on the basis of treatment received and tumour response. These originated from two randomized studies (MCD2001[1],MCD2002[2]) and a systematic review of case studies[3].

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate. Modifications in the main analysis were done from the EGP in order to capture the effect of uncertainty around the survival benefit and the impact on quality of life from Siltuximab.

Patients considered the following factors as important in the review of Siltuximab which were also relevant to the economic analysis: Control of disease symptoms (tumour recurrence, pain, rashes, lymph node swelling, loss of appetite) and reduction in hospitalizations/surgeries due to disease control (e.g. surgery to remove lymph nodes). Patients recognized the burden of IV drug delivery and were aware of the possibly of life threatening side effects. Finally the patient advocacy groups also mentioned the emotional burden of MCD extending to the family and the caregivers. However, although caregiver burden is an important aspect, according to pCODR's guidelines the submitter does not need to include the effect of the intervention on the caregiver's quality of life.

The Provincial Advisory Group (PAG) considered that the following factors would be important to consider if implementing a funding recommendation for Siltuximab, and which are relevant to the economic analysis: the size of the population (an enabler for implementation), drug wastage and the high cost of the drug (both considered barriers to implementation).

At the list price Siltuximab costs \$697.70 and \$2,790.80 per 100mg and 400mg vial respectively. At the recommended dose of 11 mg/kg IV, and by assuming a mean weight of 70kg siltuximab costs \$255.82 per day and \$7,163.05 per 28 day cycle. At the recommended dose and taking wastage into consideration, siltuximab costs \$265.79 per day and \$7444.13 per 28-day cycle. Since BSC was provided in both arms, no additional cost associated with it was assumed.

1.2 Summary of Results

A state-transition Markov model was developed by the submitter in order to support the economic analysis. This model comprised four health states: Stable Disease (SD), durable tumour and symptomatic response (CP/RP), post-treatment failure and death. The EGP, after discussions with the CGP, has conducted a number of additional analyses in order to identify the impact of uncertainty around the survival benefit and improvements in quality of life associated with siltuximab on the model outcomes.

The EGP's best estimate of the incremental cost-effectiveness ratio ($\Delta C / \Delta E$) is between \$232,663 and \$648,163 when siltuximab+BSC is compared with placebo+BSC.

These estimates should be interpreted after consideration of the large uncertainty around the evidence and the assumptions on survival and quality of life benefits.

The incremental cost-effectiveness ratio was based on an estimate of the extra cost (ΔC) and the extra clinical effect (ΔE). The EGP's best estimate of:

- The extra cost of Siltuximab is between \$195,047 and \$294,782 (ΔC).

The main factors influencing the extra cost of Siltuximab are the unit cost of siltuximab, the assumption on the life expectancy after MCD diagnosis and the duration until failure with siltuximab treatment.

- The extra clinical effect of Siltuximab is between 0.30 QALYs and 1.27 QALYs (ΔE).

The main factors influencing the extra effect are the survival benefit associated with siltuximab and the improvement in quality of life due to sustained response

The EGP based these estimates on the model submitted by Janssen Inc and reanalyses conducted by the EGP.

- Firstly, the EGP, and the CGP, felt that the assumption that there is an added survival benefit associated with siltuximab was highly uncertain. Based upon the MCD 2001 study, OS data were not mature and were only available for 1 year of follow up with no statistically significant difference between arms. The evidence supporting the assumption of a long term survival benefit modeled by the submitter was weak and originated from underpowered studies, studies with low grade of evidence (e.g. case studies), or were based on assumptions (e.g. differential survival after/before treatment failure). To assess the effect of this assumption on the outcomes of the economic analysis the EGP assumed that all the benefit of siltuximab compared to placebo is limited to the improvement in patients (preference-based) quality of life and no benefit can be observed on survival. This resulted in an estimate of QALY gain equal to 0.41 QALYs, an estimate of costs equal to \$196,729 resulting in an increase of the incremental cost-effectiveness ratio to \$482,510/QALY (from \$204.332/QALY).
- The submitter analyzed data from the MCD2001 trial to estimate the quality of life for those patients that experience tumour response, those that are in stable disease with Siltuximab or placebo as well as those that are non responders. They did so by translating SF-36 quality of life estimates to SF-6D and EQ-5D utility values. Mixed effects regression models were conducted to estimate the effects of treatment, responder status, and > Grade 2 AEs on changes in utility values over time. The submitter assumed that there is a treatment-based quality of life benefit that is independent of tumour response. This effect was further assumed to extend beyond the trial period. The latter assumption was found to be highly uncertain as treatment and response status have been found in the MCD2001 to be correlated (siltuximab patients were more likely to achieve tumour response) and the sample size was too small to provide confident estimates. Therefore, the EGP conducted additional analyses around this assumption. When the additional improvements in quality of life due to being on siltuximab treatment were restricted only to the period of the trial, the extra clinical effect of Siltuximab was 1.27 QALYs, which

increased the estimated incremental cost-effectiveness ratio to \$232,663/QALY (from \$204.332/QALY).

- The third reanalysis assumed both that no benefit on survival due to siltuximab was observed and that the, positive effect associated with receiving Siltuximab on quality of life observed, independent of response, within the MCD2001[1] trial could not be extrapolated beyond the survival period. This resulted in a reduction in the QALYs gained (0.30 QALYs) and to a decrease of the costs associated with siltuximab (\$196,729) which lead to an increase of the incremental cost-effectiveness ratio to \$648,163/QALY (from \$204.332/QALY).
- A fourth reanalysis involved reducing the time horizon of the model to 20 years. This decision was made in agreement with the CGP as it was believed that it reflects more the survival duration of patients with MCD. Reducing the time horizon in addition to the previously described changes resulted in 0.31 QALYs gained and incremental costs of \$195,047 which increased the cost-effectiveness ratio to \$629,334/QALY (from \$204.332/QALY).

The majority of the EGP's estimates were higher and more uncertain than the submitted estimates.

According to the economic analysis that was submitted by Janssen Inc., when Siltuximab +BSC is compared with placebo+BSC:

- The extra cost of siltuximab is \$294,782 (ΔC). Costs considered in the analysis included administration costs, treatment costs, routine follow-up costs and cost of adverse events.
- The extra clinical effect of siltuximab is 1.49 life-years and 1.44 QALYs gained (ΔE). The clinical effect considered in the analysis was based on extrapolations of survival after the duration of the MCD2001 [1] study and on estimates of quality of life originating from the MCD2001 [1] study.

So, the Submitter estimated that the incremental cost-effectiveness ratio ($\Delta C / \Delta E$) was \$197,269/LY or \$204.332/QALYs

1.3 Summary of Economic Guidance Panel Evaluation

If the EGP estimates of ΔC , ΔE and the ICER differ from the Submitter's, what are the key reasons?

Most of the EGP estimates were higher and included a wider range of estimates compared to those of the submitter. The main reasons were the uncertainty around the assumption of a survival benefit associated with siltuximab. The submitted study is based on short term (1 year) survival data originating from the MCD2001 [1] and MCD2002 [2] studies which were not adequately powered to observe differences in survival. The fact that the disease is rare makes identifying good estimates, especially of long term effects and costs very difficult. In this instance long term survival effects used in the economic model originate from a review of case studies (Talat et al) [3], which again can be considered a weak source of evidence. A second reason was the uncertainty around the extrapolation beyond the MCD2001 follow-up period of the independent effect of siltuximab on quality of life. Again, this effect was assumed to be observed beyond quality of life improvements due to tumor response. The small sample size that the estimates relied on as well as the

methodological limitations on the estimation method reduce the EGP's confidence on the extrapolation of this survival beyond the duration of the MCD2001[1] clinical trial. **Were factors that are important to patients adequately addressed in the submitted economic analysis?**

Factors raised by the patient advocacy group as important, such as improvements in quality of life and survival and the presence of additional side effects, were adequately addressed in the submitted economic analysis.

Is the design and structure of the submitted economic model adequate for summarizing the evidence and answering the relevant question?

Given the limitations in collecting appropriate data and focusing on hard endpoints or better established surrogate endpoints, the design and structure of the model is appropriate.

For key variables in the economic model, what assumptions were made by the Submitter in their analysis that have an important effect on the results?

This model relies on a number of assumptions for which there is little solid evidence to support them. The most important of these assumptions is that the mortality observed during the MCD2001 [1] and MCD2002 [2] studies is considered to be representative of long term mortality expected in the population. These studies are underpowered with respect to presenting an overall survival benefit. Both studies had a small sample size and were not designed to capture differences in survival. On the basis of these studies however a clear survival gain was assumed for siltuximab. In the economic model, a large share of the observed benefit of the drug originates from this assumption of survival gain.

A second assumption is that of a treatment-related, quality of life benefit that is independent of tumour response and is sustained throughout the period in which the patient is receiving treatment with siltuximab. The uncertainty associated with such extrapolation was investigated in sensitivity analyses.

Were the estimates of clinical effect and costs that were used in the submitted economic model similar to the ones that the EGP would have chosen and were they adequate for answering the relevant question?

The estimates of clinical effect and costs were similar to those that the EGP used. Given the rarity of the disease and the narrow indication population, the sources used are likely to be the most informative.

1.4 Summary of Budget Impact Analysis Assessment

What factors most strongly influence the budget impact analysis estimates?

A budget impact analysis (BIA) was submitted by Janssen inc. to quantify the impact of the introduction of siltuximab in the healthcare system. The BIA was limited to the first three years after introduction and considered costs falling on the public payer. The BIA model had to rely heavily on assumptions given the rarity of the disease. Important assumptions that can influence the outcome of the BIA include: epidemiology of the disease (incidence of MCD, proportion of patients being HIV/HHV-8 negative), duration of treatment, market assumptions.

What are the key limitations in the submitted budget impact analysis?

Although the submitter conducted a number of sensitivity analyses around the BIA estimate, one of the limitations of the BIA is its inability to take into account costs associated with the administration of the intervention. Additionally, the BIA submitted only included information that was specific to an Ontario population, with no flexibility in estimating different outcomes for different provinces. This lack of flexibility implies that provinces would have to input local estimates of incidence and prevalence to estimate a province-specific budget impact. In addition no province specific information on epidemiology was included.

1.5 Future Research

What are ways in which the submitted economic evaluation could be improved?

The economic analysis would be improved if updated estimates of overall survival were to be used from the MCD2001 [1] and MCD2002 [2] studies. In addition the model could benefit from incorporating the cost and effect of using subsequent therapies post treatment failure.

Is there economic research that could be conducted in the future that would provide valuable information related to Siltuximab for MCD?

Further research that would provide better estimates of survival and quality of life across the disease continuum would be necessary to reduce the uncertainty around the assumption made in the model.

2 DETAILED TECHNICAL REPORT

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in Section 1. Pursuant to the *pCODR Disclosure of Information Guidelines*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.

3 ABOUT THIS DOCUMENT

This Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Leukemia Clinical Guidance Panel and the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding resource implications and the cost-effectiveness of siltuximab (Sylvant) for multicentric Castleman's disease. A full assessment of the clinical evidence of siltuximab (Sylvant) for multicentric Castleman's disease is beyond the scope of this report and is addressed by the relevant pCODR Clinical Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Economic Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in the Economic Guidance Report provided to pERC for their deliberations.

This Final Economic Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Economic Guidance Report supersedes the Initial Economic Guidance Report. Note that no revisions were made in between posting of the Initial and Final Guidance Reports.

The Economic Guidance Panel is comprised of economists selected from a pool of panel members established by the pCODR Secretariat. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package and the Economic Guidance Panel Terms of Reference, which are available on the pCODR website (www.cadth.ca/pcodr). Final selection of the pool of Economic Guidance Panel members was made by the pERC Chair in consultation with the pCODR Executive Director. The Economic Guidance Panel is editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

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