pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Ofatumumab (Arzerra) for Chronic Lymphocytic Leukemia

January 29, 2015

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TABLE OF CONTENTS

1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

The main economic analysis **submitted to pCODR by GlaxoSmithKline** compared ofatumumab plus chlorambucil to chlorambucil alone for patients with chronic lymphocytic leukemia (CLL) who have not received prior therapy and for whom fludarabine treatment is considered inappropriate. Ofatumumab is administered intravenously and chlorambucil is administered orally. Ofatumumab should always be given in combination with chlorambucil in the first line setting.

According to the pCODR Clinical Guidance Panel (CGP), although this comparison is appropriate, there are also other appropriate comparators for treating patients with CLL. Other relevant comparators may be bendamustine monotherapy or rituximab plus chlorambucil. The Submitter did not include comparisons with different comparators for two reasons: 1) the clinical trial was conducted in comparison with chlorambucil; 2) an indirect comparison between ofatumumab plus chlorambucil and other trials examining potential comparators of relevance (e.g. bendamustine monotherapy or rituximab plus chlorambucil) was not possible due to large differences in the population under study.

Patients considered the following factors important in the review of ofatumumab plus chlorambucil, which are relevant to the economic analysis: increased survival, increased quality of life, and adverse events. All three of these factors have been accounted for in an adequate manner in the economic model.

The **Provincial Advisory Group (PAG)** considered that the following factors would be important to consider if implementing a funding recommendation for ofatumumab plus chlorambucil, and which are relevant to the economic analysis:

- Use of a different alkylating agent, other than chlorambucil, with ofatumumab and the impact on cost-effectiveness. The Clinical Guidance Panel confirmed there is no data to support the use of ofatumumab with other alkylating agents. This was not considered in the economic model.
- Head-to-head comparisons of ofatumumab plus chlorambucil versus other relevant comparators. There are no other existing economic models, and there is no data to support an economic model comparing ofatumumab plus chlorambucil versus another relevant comparator.
- The PAG noted that drug wastage is not a relevant factor, as ofatumumab is given as a flat dose, regardless of a patient's weight or body surface area. Dose wastage was examined in a scenario analysis in the economic model.
- Ofatumumab is administered intravenously, which is associated with increased costs such as chemotherapy chair utilization, increased pharmacy preparation and increased nursing resources. These resources were accounted for in the economic model.
- Ofatumumab has been associated with progressive multifocal leukoencephalopathy (PML). The incidence and death associated with PML was considered in the main economic analysis.
- Ofatumumab has been associated with Hepatitis B infection and reactivation. This was not considered in the economic model.

At the submitted price, ofatumumab costs $3.3600/mg and is available in a 1000mg/50mL and 100mg/5mL vial. At the recommended dose of 300 mg for the first infusion, followed

1 week later by 1000 mg on day 8, ofatumumab costs $156 per day and $4368 per 28 day cycle for the first infusion and $120.00 per day and $3360.00 per 28 day cycle for the subsequent cycles.

Bendamustine costs $312.50 and $1,250.00 per 25mg/vial and 100mg/vials. At the recommended dose of 100mg/m2 iv on days 1 & 2 every 28 days, bendamustine costs $151.79 per day and $4,250.00 per 28 day cycle.

Chlorambucil costs $1.4348 per 2mg tablet. At the recommended dose of 10mg/m^2 orally days 1-7, chlorambucil cost $3.0490 per day and $85.3706 per 28 day cycle.

1.2 Summary of Results

The EGP's best estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) is between $106,012 and $162,897 when ofatumumab plus chlorambucil is compared with chlorambucil.

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 ofatumumab plus chlorambucil is between $26,246 and $32,500. The biggest cost drivers of relevance to the best estimate are differences in drug costs, time horizon, overall survival beyond the trial period and treatment duration.
- the extra clinical effect of ofatumumab plus chlorambucil is between 0.20 and 0.25 quality adjusted life years (ΔE). The main factors affecting efficacy of relevance to the best estimate are the time horizon and overall survival beyond the trial data.

The EGP based these estimates on the model submitted by GlaxoSmithKline and reanalyses conducted by the EGP. The reanalysis conducted by the EGP using the submitted model included the following:

- The distribution of subsequent lines of therapy were taken from market research (instead of a physician survey), the extra cost of ofatumumab plus chlorambucil is $26,313 ($\Delta C_1$), which decreases the estimated incremental cost-effectiveness ratio to $64,822 (from $68,647). Using market research for the distribution of subsequent lines of therapy was felt to be a more conservative estimate since there is no Canadian data on which to draw for subsequent lines of therapy. The Clinical Guidance Panel felt that the market research data represented the current situation in Canada well.
- Only second and third line treatments are included in the economic model. This is based on input from the Clinical Guidance Panel that patients will most likely not advance to fourth line therapy. The extra cost of ofatumumab plus chlorambucil becomes $28,215 ($\Delta C_2$), which increases the estimated incremental cost-effectiveness ratio to $69,508 (from $68,647).
- Drug wastage is included, the extra cost of ofatumumab plus chlorambucil is $28,083 ($\Delta C_3$), which increases the estimated incremental cost-effectiveness ratio to $69,182 (from $68,647). Drug wastage had minimal impact on the economic model due to the method of drug administration. Drug wastage was included in order to be consistent with other therapies and pCODR reviews.

- The time horizon is shortened to 10 years from 25 years, based on input from the Clinical Guidance Panel given the life expectancy of patients with CLL from start of treatment and median age at time of diagnosis, in addition to reflecting consistency in the economic analyses of the other CLL drugs reviewed by pERC. The extra cost of ofatumumab plus chlorambucil is $26,809 and the extra clinical effect of ofatumumab plus chlorambucil is 0.25 (ΔE_2), which increases the estimated incremental cost-effectiveness ratio to $108,286 (from $68,647).
- When the above four parameters are examined together as a reanalysis (using market research for the distribution of subsequent lines of therapy, including only 2nd and 3rd line treatments, including drug wastage and a time horizon of 10 years), the extra cost and effect of ofatumumab plus chlorambucil is $26,246 ($\Delta C$) and 0.25 ($\Delta E$), which increases the estimated incremental cost-effectiveness ratio to $106,012 (from $68,647).
- Overall survival after the trial period is set to a hazard ratio of 1.0 (equal survival between the two treatments, thus, no longer extrapolating the potential benefit of ofatumumab), the extra clinical effect of ofatumumab plus chlorambucil is 0.25 (ΔE_1), which increases the estimated incremental cost-effectiveness ratio to $106,615 (from $68,647). Setting the hazard ratio to 1.0 after the time period where the clinical trial has ended reduces the uncertainty surrounding any extrapolation of data.
- When the above five parameters are examined together as a reanalysis (using market research for the distribution of subsequent lines of therapy, including only 2nd and 3rd line treatments, including drug wastage, assuming a hazard ratio of 1.0 after trial data has ended, and a time horizon of ten years), the extra cost and extra clinical effect of ofatumumab plus chlorambucil is $25,890 and 0.20, respectively, which increases the estimated incremental cost-effectiveness ratio to $129,765 (from $68,647).
- Treatment duration is assumed to be 9 months, based on input from the clinical guidance panel that, as ofatumumab is given until best response, a treatment duration of 9 months may reflect a possible "worst case scenario" in the real world clinical practice where patients are treated to 2 cycles past best response, the extra cost and extra clinical effect of ofatumumab plus chlorambucil is $34,476 and 0.41, respectively, which increases the estimated incremental cost-effectiveness ratio to $84,932 (from $68,647). Conditional funding that dictates that ofatumumab will be stopped once best response is confirmed may result in a lower ICER in the real world.
- When the above six parameters are examined together as a reanalysis (using market research for the distribution of subsequent lines of therapy, including only 2nd and 3rd line treatments, including drug wastage, a time horizon of ten years, assuming a hazard ratio of 1.0 after trial data has ended, and a treatment duration of a fixed 9 months), the extra cost and extra clinical effect of ofatumumab plus chlorambucil is $32,500 and 0.20, respectively, which increases the estimated incremental cost-effectiveness ratio to $162,897 (from $68,647).

The EGPs upper bound estimate differed from the submitted estimates.

According to the economic analysis that was submitted by GlaxoSmithKline, when ofatumumab plus chlorambucil is compared with chlorambucil in a cost-utility analysis (incremental costs per quality-adjusted life years and cost per life years gained):

- the extra cost of ofatumumab plus chlorambucil is $27,866 (ΔC). Costs considered in the analysis included drug acquisition costs, monitoring costs, administration costs, adverse event costs, and resource utilization costs for ofatumumab plus chlorambucil as well as subsequent lines of therapy.
- the extra clinical effect of ofatumumab plus chlorambucil is 0.41 quality-adjusted life years (ΔE) or 0.51 life years. The clinical effect considered in the analysis was based on overall survival, progression free survival, utility estimates and adverse events.

So, the Submitter estimated that the incremental cost-utility ratio (ΔC / ΔE) was $68,647 per quality-adjusted life year or $54,428 per life year gained.

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?

The key differences between the results of the EGP and that of the submitter's are the hazard ratio for overall survival once the trial has ended, the time horizon and treatment duration. Setting the hazard ratio to 1.0 after the trial data ended reduced the uncertainty around any extrapolation of survival benefits observed during the clinical trial. The time horizon was chosen to be 10 years, based on input from the Clinical Guidance Panel, and the median overall survival of patients from start of treatment. Further, the median age of patients starting treatment for CLL was 69 years in the clinical trial, and average life expectancy for this cohort is not expected to be 25 years (the time horizon selected by the submitter for the base case analysis). Based on feedback from the Clinical Guidance Panel, a treatment duration of 9 months was chosen to be conservative as often practice dictates continuing therapy for 2 cycles after best response. This was determined to be about 9 months.

Were factors that are important to patients adequately addressed in the submitted economic analysis?

In addition to increased survival and quality of life, patients expressed the need for options for treatment and retreatment; these were incorporated into the economic model. In terms of patient's experience with ofatumumab plus chlorambucil, two patients who responded to the survey had experience with the drug, with one of these patients experiencing adverse events. The safety profile of ofatumumab was incorporated into the model with utilities, disutilities, adverse events and costs associated with adverse events.

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

The model was transparent with many reanalyses possible. The model captured all relevant health states for this patient population and was informed by the best data available. While the structure and design of the model were adequate, there were ongoing issues with the face validity of the model over the course of the review.

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?

Major assumptions made by the submitter included the clinical data used to determine overall survival. The submitter did allow for a modification of setting the hazard ratio after the study trial ended to 1.0, reducing the uncertainty present. This was addressed in the re-analysis by the EGP. The time horizon was also identified as a key variable with an important effect on the results. The submitter had chosen a time horizon of 25 years; however, with input from the Clinical Guidance Panel, it was determined that a time horizon of 10 years is more appropriate for this population based on their overall survival at time of treatment and median age at onset of treatment (69 years in the COMPLEMENT-1 study). Finally, the assumption that chlorambucil alone is the most appropriate comparator may not reflect the current and most relevant treatment options from a clinical perspective in this population.

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 for costs provided in the economic model were adequate and inclusive. The estimates for clinical effect, however, were not felt to be appropriate. These are the overall survival following the trial period and the time horizon. These two inputs were considered in the EGP re-analysis, based on input form the Clinical Guidance Panel.

1.4 Summary of Budget Impact Analysis Assessment

What factors most strongly influence the budget impact analysis (BIA) estimates?

The BIA submitted analyzed the estimates for the increased costs in the first line setting for treating patients with CLL with ofatumumab plus chlorambucil. The agents used to determine the potential market share of ofatumumab were chlorambucil monotherapy and bendamustine monotherapy.

The BIA is most sensitive to the incidence and prevalence of CLL, the proportion of those eligible for first-line treatment with ofatumumab plus chlorambucil and treatment duration of ofatumumab. If the price of the drug were to increase, the number of patients treated were to increase, or the treatment duration were to be higher than what the submitter estimated, the increased incremental costs could be substantial. The choice of second-line treatment and the inclusion of wastage has minimal impact on the BIA results.

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

The submitter did not address subsequent lines of therapy in the BIA, nor did they address the potential role of all other current treatments used in clinical practice in this therapeutic area (for example rituximab plus chlorambucil). The BIA did not examine any scenario analyses around market share. The EGP did a re-analysis of the BIA, and doubling the market share of ofatumumab plus chlorambucil, would have a significant impact on the budget. As new agents are entering this therapeutic area, the market shares of the drugs for CLL have the potential to change rapidly, which would have the potential to significantly impact the budget. The introduction of all new potential agents, and their potential impact on market shares were not examined in a sensitivity analysis.

1.5 Future Research

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

The model provided was of high quality. There was a high level of transparency and ability to modify estimates and assumptions throughout the model. The model also incorporated many different inputs. The model could however be improved by being informed by the most relevant and current treatment options.

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

When designing clinical trials, manufacturers should consider using the current standard of care as the comparator. This would reduce the need for indirect comparisons when evaluating new drugs for reimbursement, and therefore reduce uncertainty.

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 ofatumumab (Arzerra) for chronic lymphocytic leukemia. A full assessment of the clinical evidence of ofatumumab (Arzerra) for chronic lymphocytic leukemia 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.pcodr.ca).

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.pcodr.ca). 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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