PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review Final Economic Guidance Report

Arsenic Trioxide (Trisenox) for Acute Promyelocytic Leukemia

February 18, 2014

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FUNDING

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INQUIRIES

Inquiries and correspondence about the pan-Canadian Oncology Drug Review (pCODR) should be directed to:

pan-Canadian Oncology Drug Review
1 University Avenue, suite 300
Toronto, ON
M5J 2P1

Telephone: 416-673-8381
Fax: 416-915-9224
Email: info@pcodr.ca
Website: www.pcodr.ca

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

The submitter is requesting funding for arsenic trioxide for two separate groups of patients: those with newly diagnosed acute promyelocytic leukemia (APL) (low, intermediate and high risk patients) and those with refractory/relapsed APL.

- The main economic analysis for newly diagnosed APL patients **submitted to pCODR by Lundbeck Canada Inc.** compared arsenic trioxide (ATO) plus all-trans retinoic acid (ATRA) to ATRA plus idarubicin (IDA) in newly diagnosed patients with acute promyelocytic leukemia for low-intermediate risk patients. The manufacturer also provided an economic analysis which examined the cost-utility of the early addition of ATO to ATRA plus danorubicin in high risk patients.
- The main economic analysis for refractory/relapsed APL patients **submitted to pCODR to Lundbeck Canada Inc.** compared ATO to ATRA plus chemotherapy in patients with relapsed/refractory APL.

Arsenic trioxide is administered intravenously while ATRA is administered orally, and IDA and comparator chemotherapy is administered intravenously.

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate for both newly diagnosed and relapsed/refractory patients. The Submitter also provided a complementary analysis that included the comparison of ATO+ATRA to ATRA+IDA+ARA-C, which was also deemed relevant but was appropriate as a complementary analysis given its less frequent use.

It should be noted that the total amount of ATRA, though used in both the intervention and comparator, is different depending on the regimen. In newly diagnosed low risk patients, for the ATO+ATRA regimen, during induction ATRA is dosed at 45 mg/m2 daily until complete remission; during consolidation ATRA is dosed at 45 mg/m2 daily, 2 weeks on / 2 weeks off for a total of 7 courses. For the ATRA+IDA regimen: during induction, ATRA is given at 45 mg/m2 daily until complete remission; however, during consolidation, ATRA is given 45 mg/m2 daily for 15 days, for a total of 3 courses. For the ARA-C+IDA+ATRA regimen, during induction ATRA is given at 45 mg/m2 daily; during consolidation, ATRA is maintained at 45 mg/m2 daily. In newly diagnosed high risk patients, there is no difference in the administration of ATRA during either the induction or consolidation period. In relapsed/refractory patients, ATRA was not considered in the ATO regimen. The costs of these differing drug regiments are considered in the model.

Patient advocacy group input considered the following factors important in the review of arsenic trioxide, in addition to access to a non-chemotherapy based treatment, which are relevant to the economic analysis: fewer treatment induced side-effects (rashes, mouth sores, temporary blindness, sweats, bone pain, frequent infections, extreme headaches) and fewer long-term side effects (life-changing fatigue, memory issues, decreased quality of life and infertility). The economic model considered adverse events, though these adverse events were not measured directly from patients with APL. A full summary of the patient advocacy group input is provided in the pCODR Clinical Guidance Report.

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

- daily one-hour intravenous infusions. The economic model took into consideration the additional chair time or hospital admission due to drug administration (though this was done via an assumption as no data is directly available for arsenic trioxide).
- monitoring for serious events listed in the black box warning. Serious events were considered to occur in the induction period and any associated costs of these adverse events were included as part of hospitalization in the induction period in the economic model.

A full summary of the PAG input is provided in the pCODR Clinical Guidance Report.

At the submitted list price, arsenic trioxide costs $530 per 10 mg single-use ampoule. During induction, at the recommended dose of 0.15 mg/kg/day until complete remission or a maximum of 60 doses, arsenic trioxide costs $556.50 per day and $15,582 per 28-day course. During consolidation, at the recommended dose of 0.15 mg/kg/day for 5 days per week for four weeks every 8 weeks (for a total of 90 treatments), arsenic trioxide costs $397.5 per day and $11,130 per 28-day cycle.

ATRA costs $13.11 per 10mg capsule. At the recommended dose of 45 mg/m^2/ day, ATRA costs $100.29 per day and $2,808.16 per 28-day course.

1.2 Summary of Results

1.2.1 Newly diagnosed (first line) setting

Low/intermediate risk patients

The EGP's best estimate of the incremental cost-utility ratio (ΔC / ΔE) is about $53,112 when arsenic trioxide plus all-trans retinoic acid is compared with all-trans retinoic acid plus idarubicin and the outcome is cost per quality-adjusted life years. The most significant cost drivers of the model are drug administration costs (for either treatment), and mortality risks after relapse. Clinical effects for low-intermediate risk patients were based on the Lo-Coco study.

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 in the first-line setting of:

- the extra cost of arsenic trioxide is between $76,393, mostly due to the increased cost of the drug and drug administration costs.
- the extra clinical effect of arsenic trioxide is 1.44 quality-adjusted life years (ΔE), due to the increased survival of patients treated with this drug.

The EGP based these estimates on the model submitted by Lundbeck Canada Inc. and reanalyses conducted by the EGP. The reanalysis conducted by the EGP using the submitted model showed that when:

- wastage is included in the economic model as a modified analysis, the extra cost of arsenic trioxide is $76,393 ($\Delta C_1$), which increases the estimated incremental cost-effectiveness ratio. The EGP included wastage in the economic model as arsenic trioxide is administered intravenously, and given that it is a uncommon disease, it is very unlikely that more than one patient will be treated at the same time at the same

center, thus leading to the potential of having unused ampoules during a given treatment course.

- the EGP examined increased drug administration costs as a modified analysis. If only the drug administration costs for ATO+ATRA were increased by 25%, the extra cost of arsenic trioxide would be $91,151. Although the PAG noted concerns about increased drug administration costs, the EGP considered that the assumptions made by the submitter in the model were reasonable and that no increases were warranted as part of the EGPs best estimate.
- Although the Clinical Guidance Panel considered the included studies the best available data, given the limited data and number of trials in this area, the EGP examined increasing the number of clinical events as a modified analysis to explore the robustness of the model. If the number of events in the ATO+ATRA group were to be doubled, the extra cost of arsenic trioxide would be $75,521.

The EGPs estimates were similar to, but marginally higher, than the submitted estimates.

According to the economic analysis that was submitted by Lundbeck Canada Inc., when arsenic trioxide plus all-trans retinoic acid (ATRA) is compared with ATRA plus idarubicin in **low-intermediate risk patients**, the incremental cost-utility analysis found that:

- the extra cost of arsenic trioxide is $72,194 (ΔC). Costs considered in the analysis included treatment costs, drug administration costs, cost of salvage therapy, and medical costs during follow-up.
- the extra clinical effect of arsenic trioxide is 1.44 quality-adjusted life years (ΔE) or 1.56 life years gained. The clinical effect considered in the analysis was based on event-free survival, post-failure survival, the incidence of adverse events, utilities and disutilities.

So, the Submitter estimated that the incremental cost-utility ratio (ΔC / ΔE) was $50,193 per QALY or $46,361 per life year.

<u>High risk patients</u>

The EGP's best estimate of the incremental cost-utility ratio (ΔC / ΔE) is about $22,102 when the addition of arsenic trioxide is used in consolidation compared with standard consolidation (all-trans retinoic acid plus ARA-C plus daunorubicin) in high-risk patients and the outcome is cost per quality-adjusted life years. The most significant cost drivers of the model are the cost of salvage therapy, and utilities for health states. Clinical effects for high risk patients were based on the Powell study.

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 arsenic trioxide is between $7,185, mostly due to the increased cost of the drug and drug administration costs.
- the extra clinical effect of arsenic trioxide is 0.33 quality-adjusted life years (ΔE), due to the increased survival of patients treated with this drug.

According to the economic analysis that was submitted by Lundbeck Canada Inc., when arsenic trioxide was added to **standard consolidation therapy (all-trans retinoic acid plus ARA-C plus daunorubicin)** in **high risk patients**:

- the extra cost of the addition of arsenic trioxide is $4,780 (ΔC).Costs considered in the analysis included treatment costs, drug administration costs, and medical costs during follow-up.
- the extra clinical effect of the addition of arsenic trioxide is 0.33 quality-adjusted life years (ΔE). The clinical effect considered in the analysis was based on event-free survival, post-failure survival and utilities. Clinical effects were derived from the Powell study.

So, the Submitter estimated that the incremental cost-utility ratio (ΔC / ΔE) was $14,703 per QALY.

1.2.2 Relapsed / refractory (2nd line setting) patients

The EGP's best estimate of the incremental cost-utility ratio (ΔC / ΔE) is between $13,798 and $82,161 when arsenic trioxide is compared to all-trans retinoic plus chemotherapy. The most significant cost drivers of the model are the health state utilities, drug administration costs (for either treatment), and the percentage of patients receiving stem cell transplantation after relapse. The treatment regimens for the two groups were taken from two separate publications (Soignet et al. 2001 for ATO [1] and Thomas et al. 2000 for ATRA+CT[2]) as there is no trial directly comparing ATO and ATRA+CT in this setting. The Soignet study was included in the pCODR systematic review of arsenic trioxide in the relapse/refractory setting and the Thomas study is summarized as supporting literature in section 2.1.4 of the pCODR Clinical Guidance Report. The CGP considered these studies provided a reasonable basis for clinical inputs in the economic model. However, these were both single arm studies and other studies evaluating arsenic trioxide in the relapse/refractory setting were included in the pCODR systematic review.

The incremental cost-utility ratio was based on an estimate of the extra cost (ΔC) and the extra clinical effect (ΔE). The EGP's best estimate in the relapse/refractory setting of:

- the extra cost of arsenic trioxide, which is between -$2,556 and $39,212, mostly due to the increased cost of the drug and drug administration costs.
- the extra clinical effect of arsenic trioxide, which is between -1.42 and 1.87 quality-adjusted life years (ΔE), due to the varying increased survival of patients treated with this drug.

The EGP based these estimates on the model submitted by Lundbeck Canada Inc. and reanalyses conducted by the EGP. The reanalysis conducted by the EGP using the submitted model showed that when:

- wastage is included in the economic model as a modification to the main analysis, the extra cost of arsenic trioxide is $39,212 ($\Delta C_1$), which increases the estimated incremental cost-utility ratio. The EGP included wastage in the economic model as arsenic trioxide is administered intravenously, and given that it is an uncommon disease, it is very unlikely that more than one patient will be treated at the same time

at the same center, thus leading to the potential of having unused ampoules during a given treatment course.

- as the PAG identified that drug administration costs may be a concern, the EGP analyzed a 25% increase in drug administration costs in the outpatient setting for ATO only. This increase in drug administration costs increased the cost of arsenic trioxide to $58,097. However, the assumptions made by the submitter seem adequate and the EGP did not consider it was necessary to increase the costs of drug administration in the best case estimate.
- the EGP considered increased mortality after relapse as a modification, as the submitter made the assumption that mortality after 2 years was similar to that of the general population, for both treatment arms. However, an increased mortality of 25% in *only* the ATO treatment arm decreased the effectiveness by an additional 0.13, and increased the ICER to $22,532. With guidance for the CGP, the EGP did not feel that an increased mortality risk should be part of their best case estimate.
- Given that the studies included were single-arm studies, the EGP considered modified analyses varying the survival estimates from other studies examining the use of ATO in the relapsed/refractory study. The manufacturer provided a complementary analysis that included survival estimates from three studies (Soignet 1998, Soignet 2001, Lazo 2003). If estimates were used from Soignet et al. 1998 [3], the extra cost of arsenic trioxide is $35,809, and the extra clinical effect is 0.45 QALYs, which results in an incremental cost-utility ratio of $80,263. If estimates were used from Lazo et al.[4], the extra cost of arsenic trioxide is $32,148, and the extra clinical effect is 2.41 QALYs, which results in an incremental cost-utility ratio of $13,338. A pooled analysis of the 3 studies provided by the manufacturer was not incorporated into the EGP reanalyses because the generalizability was uncertain.
- As utilities were a cost driver in this model, the EGP analyzed a decrease in utility values for the induction period only. This made almost no impact on the ICER and therefore was not considered in the best case estimate of the EGP.

The EGPs estimates differed from the submitted estimates, although the range provided by the EGP includes the ICUR submitted by the manufacturer.

According to the economic analysis that was submitted by Lundbeck Canada Inc., when arsenic trioxide is compared with ATRA plus chemotherapy:

- the extra cost of arsenic trioxide is $38,188 (ΔC). Costs considered in the analysis included treatment costs, drug administration costs, cost of salvage therapy, and medical costs during follow-up.
- the extra clinical effect of arsenic trioxide is 1.87 quality-adjusted life years or 1.55 life years (ΔE). The clinical effect considered in the analysis was based on event-free survival, post-failure survival, the incidence of adverse events, utilities and disutilities.

So, the Submitter estimated that the incremental cost-utility ratio (ΔC / ΔE) was $20,443 per QALY or $24,352 per LY.

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 EGP estimates in cost for arsenic trioxide in both the newly diagnosed and relapsed/refractory patient setting were higher because the EGP considered wastage in their best case estimate. This was based on the fact that APL is an uncommon disease, and it is unlikely that two patients with APL would be treated at the same center at the same time, thus creating wastage from unused ampoules. Though some ampoules can be re-used the next day, in the consolidation phase of treatment, the course of the treatment is 5 days on, and the prepared solution from Friday would not be able to be re-used for Monday (48 hour shelf life). Further, in the relapsed/refractory patient setting, as there was no randomized controlled trial, the EGP felt that a range of estimates best reflected the uncertainty in the results.

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

Yes, the most important factor identified by patients was to reduce side-effects from chemotherapy-based drugs. The economic models did include adverse events. However, given APL is an uncommon cancer, these adverse events were based on a study for acute myeloid leukemia (AML). The CGP indicated that this was an adequate assumption.

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

Yes, the submitter provided a well-designed Markov model, in Excel, that was transparent and easy to manipulate, and included reasonable inputs. The model captured the relevant health states and was informed with the best data available. The EGP was able to modify all estimates and assumptions with the model provided, thereby assessing any inputs.

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?

For newly diagnosed patients with APL, the cost drivers were drug administration costs and mortality risk after relapse. As data was not available for the drug administration costs of APL, the submitter assumed that these costs were similar to fludarabine. The CGP confirmed that this assumption was adequate. The second assumption that impacted costs, was the assumption that the risk of relapse in patients after 4 years was the same as that of the general population. The CGP confirmed that this assumption was adequate in for these patients, as patient survival is quite good.

In the relapsed/refractory setting for patients with APL, the following assumptions were made: utilities of health states during induction, drug administration costs, and mortality risk after second relapse. The majority of the utilities of health states were taken from a study on AML, however, the health state utility for induction was an assumption on behalf of the submitter that was verified by clinical opinion. Upon examination in a modified analysis, this health state utility did not have an effect on the results. The same assumptions for drug administration costs were made as in the first line setting (see

above). One final assumption made on behalf of the submitter was the risk of mortality in patients who experience a second relapse. These patients were assumed to have the same mortality risk as the general population two years after commencing treatment. Though there is little data in this area, the CGP concluded that this is a plausible estimate. Further, the economic model submitted had these assumptions for both treatment arms.

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?

Yes, the estimates for clinical effects and costs were well chosen, based on the availability of data. In the first line setting, the clinical data was based on a phase III clinical trial. In the relapsed / refractory setting, the clinical data was based on an indirect comparison, and the best available data was from single arm studies as no randomized controlled trials were available. This evidence, though the best available, has limitations and increased uncertainty. The submitter provided survival estimates from three single-arm studies although other single-arm studies were also available in the literature. The CGP was consulted to provide feedback on all assumptions and estimates included in the economic model and key clinical studies were included in the systematic review.

1.4 Summary of Budget Impact Analysis Assessment

What factors most strongly influence the budget impact analysis estimates?

In newly diagnosed patients, the BIA submitted is based on treatment of a small number of patients per year in the first line setting ([redacted]% of first line cases), as APL is uncommon. The estimate on the number of patients to be treated in the first line setting is supported by the CGP. The Provincial Advisory Group identified that if funding for arsenic trioxide were to be approved, the number of patients in the first line setting would be larger than the relapse setting, which could be a barrier to implementation. *(Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed.)*

In the relapsed / refractory patient setting, the BIA is based on fewer patients per year than in the first line setting, which is supported by the CGP, and assumed that all patients in this setting would be treated with ATO. The Provincial Advisory Group identified that many patients are accessing arsenic trioxide through the special access group currently and that this treatment would fill a much needed gap. The BIA submitted is in line with this.

In both the newly diagnosed setting and the relapsed / refractory setting, if the price of the drug were to increase, or the number of patients treated were to increase, the increased incremental costs could be substantial depending on the magnitude of the increase.

In the first line setting, increasing the market share does not impact the results. In the relapsed setting, should the market share decrease, the BIA will decrease.

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

The submitter conducted several modified analyses to examine the impact of various scenarios on the costs if arsenic trioxide were to be funded. These include a longer induction period, a growth in incidence of the disease and a higher relapse rate.

1.5 Future Research

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

Though no improvements could be identified for the design and structure of the submitted model, more data for clinical inputs, especially in high-risk patients, would increase the generalizability and confidence of the estimates of the results, especially when events are uncommon. Further, in the relapsed/refractory setting, data was based on single-arm studies; randomized controlled trials, including direct comparison randomized controlled trials would increase the confidence in the estimates of the data. However, the EGP recognizes the challenge of reproducing trial data in a population of patients with an uncommon disease. In the future, a pooled estimate on all available single-arm studies could decrease the uncertainty of the estimates.

Is there economic research that could be conducted in the future that would provide valuable information related to arsenic trioxide for acute promyelocytic leukemia?

Though not always feasible, direct measurements of utilities are ideal. Future clinical trials in this area should consider collecting this information alongside clinical data.

2 DETAILED TECHNICAL REPORT – Low/Intermediate Risk Disease

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3 DETAILED TECHNICAL REPORT – High Risk Disease

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4 ABOUT THIS DOCUMENT

This Final Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Lukemia 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 Arsenic Trioxide (Trisenox) for Acute Promyelocytic Leukemia. A full assessment of the clinical evidence of Arsenic Trioxide (Trisenox) for Acute Promyelocytic 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*. The manufacturer, as the primary data owner, did not agree to the disclosure of some economic information, therefore, this information was redacted from this publicly available Guidance Report.

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 Economic Guidance Report.

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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