pCODR EXPERT REVIEW COMMITTEE (pERC)
INITIAL RECOMMENDATION

The pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug-funding decisions. The pCODR process brings consistency and clarity to the cancer drug assessment process by looking at clinical evidence, cost-effectiveness and patient perspectives.

Providing Feedback on this Initial Recommendation
Taking into consideration feedback from eligible stakeholders, the pERC will make a Final Recommendation. Feedback must be provided in accordance with *pCODR Procedures*, which are available on the pCODR website. The Final Recommendation will be posted on the pCODR website once available, and will supersede this Initial Recommendation.

Drug:
Arsenic trioxide (Trisenox)

Submitted Funding Request:
For patients who were refractory to or relapsed from previous treatment and newly diagnosed APL patients who have received no prior treatment

Submitted By:
Lundbeck Canada Inc.

Manufactured By:
Lundbeck Canada Inc.

NOC Date:
June 7, 2013

Submission Date:
August 30, 2013

Initial Recommendation Issued:
January 30, 2014

pERC RECOMMENDATION	The pCODR Expert Review Committee (pERC) recommends funding arsenic trioxide (ATO; Trisenox) in combination with all trans-retinoic acid (ATRA) in the **first-line setting** as a treatment for the induction of remission and/or consolidation of low to intermediate risk acute promyelocytic leukemia (APL) and as a consolidation treatment for high risk APL after induction with ATRA plus chemotherapy for patients with the t(15;17) translocation and PML/RAR-alpha gene expression. The Committee made this recommendation because there was a net overall clinical benefit of arsenic trioxide in this setting, because it aligns with patient values and because it is considered cost-effective in this setting. pERC also recommends funding arsenic trioxide (ATO; Trisenox) as a treatment for the induction of remission and consolidation in patients with APL who **have relapsed** after completion of first-line therapy, including ATO-based regimens, or who have **disease refractory to** non-ATO based regimens, for patients with the t(15;17) translocation and PML/RAR-alpha gene expression. The Committee made this recommendation because pERC concluded that there is a net overall clinical benefit of arsenic trioxide in this setting, because it aligns with patient values and because it is considered cost-effective in this setting. pERC considered that a randomized controlled trial was not thought to be feasible in the relapsed/refractory setting as APL is uncommon and only a small proportion of these patients relapse after completing first-line therapy.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	No next steps were identified.

SUMMARY OF pERC DELIBERATIONS

pERC discussed that in the first-line setting, patients with acute promyelocytic leukemia (APL) are treated with all trans-retinoic acid (ATRA) and anthracycline-based chemotherapies but in the relapsed/refractory setting there are no other effective treatment options. pERC also noted there are important short-term and long-term toxicities associated with ATRA and these chemotherapies including APL differentiation syndrome, second primary malignancies, cardiomyopathy and myelodysplasia. Therefore, pERC considered that there is a need for treatments with an improved toxicity profile in the first-line setting and an even greater need for effective therapies in the relapsed/refractory setting. pERC also discussed the burden of illness of APL and noted that this is a very uncommon cancer. It was discussed that approximately 20% of patients relapse after first-line therapy; therefore, the number of patients to be treated in the relapsed setting would be even smaller than in the first-line setting.

pERC's *Deliberative Framework* for drug funding recommendations focuses on four main criteria:	
CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

The pCODR systematic review included three randomized controlled trials evaluating arsenic trioxide in the first-line setting (Lo-Coco 2013, Powell 2010, Shen 2004) and 11 prospective cohort studies in the relapsed/refractory setting.

In the first-line setting, pERC concluded that there is a net clinical benefit of arsenic trioxide for patients with low to intermediate risk APL as an induction and consolidation treatment (based on the Lo-Coco study) and for patients with high-risk APL as a consolidation treatment after induction with ATRA and chemotherapy (based on the Powell study). pERC discussed that, in the Lo-Coco study, two-year event-free survival rates were significantly greater in the ATRA plus arsenic trioxide group compared with the ATRA plus chemotherapy group (97% versus 86%). Similarly, in the Powell study, the three-year event-free survival rates were greater in the ATRA plus chemotherapy plus arsenic trioxide group compared with the ATRA plus chemotherapy group (80% versus 63%). pERC noted there was no evidence for the use of arsenic as part of induction therapy in patients with high-risk APL. pERC discussed that, from a clinical perspective, these results suggest a long-term benefit or possible cure for APL and demonstrate the efficacy of arsenic trioxide in the first-line setting.

In the relapsed/refractory setting, pERC concluded that there is a net clinical benefit of arsenic trioxide for patients who have relapsed after any previous first-line therapy and for patients who are refractory to non-arsenic trioxide therapies. pERC discussed that the 11 studies varied in key details such as the population characteristics, treatment protocols, and outcomes measured. However, pERC noted that there was a consistently strong signal of arsenic trioxide activity across all studies, as complete remission rates ranged from 71% to 100%, with a median rate of 85%. pERC noted that randomized controlled trials comparing arsenic trioxide to other treatments were not available in this setting. However, pERC agreed that non-randomized, non-comparative evidence was acceptable in this situation because the feasibility of conducting a randomized controlled trial would be very low given the small number of relapsed/refractory patients with APL. Although pERC noted that there is some uncertainty in the precise magnitude of the benefit, the consistently high complete remission rates across multiple studies led pERC to conclude that there is an overall net clinical benefit of arsenic trioxide. pERC considered that, when taken together, the body of evidence from these studies supports the efficacy of arsenic trioxide in the relapsed and refractory settings.

pERC discussed the toxicity profile of arsenic trioxide in both the first-line and relapsed/refractory settings. Overall, pERC considered it to be acceptable and distinct from the toxicities associated with ATRA and anthracycline-based chemotherapies. Generally, in studies that provided comparative data, fewer deaths were observed with arsenic trioxide than with ATRA and/or chemotherapy. The most common causes of death with comparator therapies included APL differentiation syndrome, hemorrhagic shock, bronchopneumonia and intracerebral hemorrhage. pERC discussed that APL differentiation syndrome is a serious harm associated with APL treatment that must be treated immediately to prevent

death. pERC noted that QT prolongation was observed more frequently with arsenic trioxide and would require close monitoring. pERC noted that induction therapy is generally administered in-hospital while consolidation therapy is administered on an out-patient basis. Because of the potential for serious harms, pERC considered that patients would need to be treated in specialized centres and monitored for adverse events. pERC also noted that the trials had only a short follow-up period and could not provide information on long-term harms.

pERC deliberated upon the alignment of arsenic trioxide with patient values in both the first-line and relapsed/refractory settings. It was noted that patients are seeking less toxic treatments that are as effective as or more effective than current therapies. Therefore, pERC considered that arsenic aligned with these patient values based on the efficacy and toxicity profile observed in the arsenic studies included in the pCODR review. In addition, it was noted that functional outcomes and quality of life (e.g. fatigue) were very important to patients with APL. However, none of the first-line or relapsed/refractory studies measured quality of life. pERC considered this a very important outcome, particularly when the toxicity profile of treatments such as ATRA and anthracycline-based chemotherapies are concerning. Therefore, pERC was limited in its ability to determine how arsenic trioxide aligns with this patient value. However, pERC noted that access to arsenic trioxide could improve quality of life for patients as they could potentially avoid the toxic effects associated with ATRA and/or anthracycline-based chemotherapies.

pERC deliberated upon the cost-effectiveness of arsenic trioxide and discussed the pCODR Economic Guidance Panel's (EGP) appraisal of the submitted economic evaluation. They noted that the economic model was highly transparent and the EGP was able to modify all of the key parameters in the model. In the first-line setting, pERC discussed that the EGP and the manufacturer's estimates of cost-effectiveness were similar and both were considered within an acceptable range. In the relapsed/refractory setting, pERC discussed the range of incremental cost-effectiveness ratios (ICER) provided by the EGP. pERC discussed that the uncertainty in the ICER was primarily due to the uncertainty in the clinical data provided by the single arm studies. However, it was noted that the manufacturer's estimate was within the EGP's range, which was considered acceptable. pERC also discussed that wastage of arsenic trioxide could slightly increase the ICERs but that the impact of wastage could likely be reduced in clinical practice, for example, if centres used extended stability for arsenic trioxide. Therefore, pERC concluded that at the submitted price, arsenic trioxide is cost-effective in both the first-line and relapsed/refractory settings.

pERC discussed the feasibility of implementing a funding recommendation for arsenic trioxide. pERC discussed input from pCODR's Provincial Advisory Group on the use of arsenic trioxide in children. It was noted that some studies in the systematic review allowed for the inclusion of children. Despite the small number of children in these studies, pERC considered this was reasonable for an uncommon disease such as APL and that the underlying pathogenesis of APL is similar in adults and children. Therefore, pERC considered that the results were generalizable to a pediatric population. pERC also discussed that most studies had an upper age limit for enrollment. However, pERC considered that this was likely done to prevent exposure of older adults to the toxicities associated with the aggressive chemotherapy in the comparator arm(s) and that the use of arsenic trioxide, which does not have these toxicities, would be reasonable in an older population.

pERC also discussed the potential impact of arsenic trioxide on current treatment algorithms. Amongst studies conducted in the relapsed setting, at least one of the studies (Wang 2004) included patients who had received prior treatment with arsenic trioxide in the first-line setting. pERC discussed that currently some patients could be receiving arsenic trioxide re-treatment in the relapsed setting if they had received arsenic trioxide as a first-line treatment through special access programs and that this practice would likely become more common as arsenic trioxide becomes more accessible. Therefore, pERC agreed with the pCODR Clinical Guidance Panel that re-challenge with arsenic trioxide in patients who relapse following completion of first-line therapy with arsenic trioxide would be reasonable from a clinical perspective.

EVIDENCE IN BRIEF

pERC deliberated upon a pCODR systematic review, other literature in the Clinical Guidance Report providing clinical context, an evaluation of the manufacturer's economic model and budget impact analysis, guidance from pCODR clinical and economic review panels, input from one patient advocacy group(Leukemia & Lymphoma Society of Canada, LLSC) and input from pCODR's Provincial Advisory Group.

OVERALL CLINICAL BENEFIT

pCODR review scope

To evaluate the effectiveness of arsenic trioxide (ATO), as monotherapy or in combination with other chemotherapy agents, on patient outcomes compared with appropriate comparators for the treatment of patients with:

- Previously untreated (first-line) acute promyelocytic leukemia (APL).
- Relapsed/refractory APL

Studies included: randomized controlled trials in first line, but not relapsed/refractory

In the first line setting, the pCODR systematic review included 3 randomized controlled trials (Lo-Coco 2013, Powell 2010, Shen 2004).

- Lo-Coco 2013 evaluated the non-inferiority of ATO plus ATRA (n=77) in comparison to chemotherapy plus ATRA (n=79) as an induction and consolidation treatment for patients with low to intermediate risk APL;
- Powell 2010 evaluated consolidation of ATRA plus chemotherapy with (n=244) or without ATO (n=237) after induction with ATRA and chemotherapy, for patients in all risk categories of APL
- Shen 2004 evaluated ATO (n=20), ATRA (n=20) and ATO plus ATRA (n=21) as induction therapy. There were limitations in the Shen study in terms of the sample size, generalizability of the patient population, lack of information on the randomization and blinding and unclear reporting of results that created significant uncertainty in the comparability of Shen 2004 to the two other included studies. Therefore it was not discussed in detail by pERC.

In the relapsed/refractory setting, the pCODR systematic review included eleven prospective studies (Wang 2004, Raffoux 2004, Alimoghaddam 2011, Lazo 2003, Niu 1999, Shen 2001, Shen 1997, Shigeno 2005, Soignet 2001, Soignet 1998, Yanada 2013). Of these studies, Wang 2004 included both a prospective ATO monotherapy arm and a comparative historical cohort treated with ATRA. The sample size ranged from 12 to 47 patients across all studies and the follow-up period was short for all included studies. The study characteristics were variable and each incorporated ATO in different combinations with other agents and at different stages of treatment (e.g. induction, consolidation or both). pERC considered that the variability among studies in terms of patient characteristics, treatment protocols and measurement of outcomes made comparability of the different studies challenging.

The pCODR review also provided contextual information from Thomas et al 2000, on comparators in the relapsed/refractory setting.

Patient populations: reasonable for treatment across different risk categories and ages

In the first line setting, the Powell study included low, intermediate and high risk patients as defined by their white blood cell counts while the Lo-Coco study included only patients with low to intermediate risk APL. pERC discussed that patients with high risk APL have a worse prognosis than other lower risk patients; therefore, it was reasonable to expect lower responses in the high risk patients. pERC also discussed that due to the different treatment protocols evaluated in the Lo-Coco and Powell studies, there is currently no evidence for the use of ATO as an induction treatment in patients with high-risk APL.

Although none of the included studies in either the first-line or relapsed/refractory setting were conducted solely in a pediatric population, many studies allowed for both children and adults to be included. pERC also noted that given the similar pathogenesis of the disease in patients of all age groups, the results of the adult studies could be generalized to children.

pERC also discussed the use of previous treatments in patients who had relapsed following completion of first-line therapy.

Key efficacy results in the first line setting: high and statistically significant event-free survival rates

In the first-line setting, the key efficacy outcomes deliberated on by pERC were overall survival and event-free survival (EFS), which was the primary outcome in both the Lo-Coco and Powell studies. pERC concluded that there is a net clinical benefit of arsenic trioxide for patients with low to intermediate risk APL as an induction and consolidation treatment (based on the Lo-Coco study) and for patients with high-risk APL as a consolidation treatment (based on the Powell study). It was noted that 2 year overall survival rates in the Lo-Coco study favoured arsenic trioxide compared with the control group (99% versus 91%, respectively, p=0.02) while 3-year overall survival rates in the Powell study were not statistically significantly different between groups (86% versus 81%, respectively, p=0.07). pERC discussed that, in the Lo-Coco study, two-year event-free survival rates were significantly greater in the ATRA plus arsenic trioxide group compared with the ATRA plus chemotherapy group (97% versus 86%, respectively, p<0.001 for non-inferiority and P=0.02 for superiority). Similarly, in the Powell study, three-year event-free survival rates were greater in the ATRA plus chemotherapy plus arsenic trioxide group compared with the ATRA plus chemotherapy group (80% versus 63%, respectively, p<0.001). Overall, pERC discussed that, from a clinical perspective, these results suggest a long-term benefit or possible cure and demonstrate the efficacy of arsenic trioxide in the first-line setting. Subgroup analyses of event-free survival rates in the Powell study demonstrated no statistically significant differences between the high-risk group and the low to intermediate risk group. pERC noted there was no evidence for the use of arsenic as an induction therapy in patients with high-risk APL.

Key efficacy results in the relapsed/refractory setting: consistently strong complete remission rates

In the relapsed/refractory setting the key efficacy outcome deliberated on by pERC was complete remission (CR), which was the primary outcome in most studies. pERC concluded that there is a net clinical benefit of arsenic trioxide for patients who have relapsed after any previous first-line therapy and for patients who are refractory to non-arsenic trioxide therapies. pERC discussed that the 11 studies varied in key details such as the patient characteristics, treatment protocols and outcomes measured. However, pERC noted that there was a consistently strong signal of activity across all studies; complete remission rates ranged from 71% (Wang 2004) to 100% (Lazo, 2003), with a median rate of 85%. In the Wang study, which evaluated ATO but also included a historical cohort of ATRA alone, CR was 71% versus 20%, respectively (p<0.05). pERC discussed that randomized controlled trials comparing arsenic trioxide to other treatments were not available in this setting. However, pERC agreed that non-randomized evidence was acceptable in this situation because the feasibility of conducting a randomized controlled trial would be very low given the small number of relapsed/refractory patients with APL. Therefore, pERC considered that, when taken together, the results from this body of evidence supported the efficacy of arsenic trioxide in the relapsed and refractory settings.

Quality of life: important to patients but not reported in any studies

Quality of life was not reported in any of the first-line or relapsed/refractory studies**.** pERC considered this a very important outcome, given concerns with the toxicity profile of treatments such as ATRA and anthracycline-based chemotherapies. Patient advocacy group input also indicated that quality of life was important to patients. Because of the lack of data from the included studies, pERC was unable to determine the effect of arsenic trioxide on quality of life. However, pERC noted that access to arsenic trioxide could improve quality of life for patients as they could potentially avoid the toxic effects associated with ATRA and/or anthracycline-based chemotherapies.

Safety: acceptable and distinct toxicity profile compared with ATRA and anthracycline-based chemotherapies

pERC discussed the toxicity profile of arsenic trioxide in both the first-line and relapsed/refractory settings. Overall, pERC considered it to be acceptable and distinct from the toxicities associated with ATRA and anthracycline-based chemotherapies.

Generally, in studies that provided comparative data, fewer deaths were observed with arsenic trioxide than in the ATRA or chemotherapy groups. Fewer deaths were reported in the ATO group compared with

the chemotherapy group in the Lo-Coco study (1 versus 7 patients, respectively) with the most common causes of death being APL differentiation syndrome, hemorrhagic shock and bronchopneumonia. The Powell study reported similar number of deaths in both arms however subgroup analysis by risk group showed that more deaths occurred in high risk patients with 4%, 4% and 20% of deaths occurring in the low, intermediate and high risk groups, respectively. In the relapsed/refractory setting, deaths were reported in all studies ranging from 3% to 41% of patients. In the Wang study, fewer patients died in the ATO plus ATRA group compared with the historical cohort who received ATRA alone (33.3% vs 7.4%, respectively p>0.05).

pERC also discussed specific adverse events observed in patients with APL. The most frequent toxicities resulting in dose modifications were neuropathy, cardiac toxicity, retinoic acid syndrome, APL differentiation and major organ dysfunction. pERC noted that QT prolongation was observed more frequently with arsenic trioxide and would require close monitoring as it can be managed appropriately by oncologists when detected. The Powell study reported QT prolongation in 16% versus 0% of patients in the ATRA plus chemotherapy plus ATO group versus ATRA plus chemotherapy, respectively, (p<0.001), while Lo-Coco reported no events in any patients. pERC discussed that the APL differentiation syndrome is a serious harm associated with APL treatment that must be treated immediately to prevent death. In the first line setting, APL differentiation syndrome occurred in 37% of patients during induction in the Powell study, while no difference was reported in the Lo-Coco study. pERC considered, the occurrence of APL differentiation syndrome and hyperleukocytosis to be acceptable in the included studies. However, because of the potential for serious harms, pERC discussed that patients would need to be treated in specialized centres and monitored for adverse events. With appropriate monitoring and early treatment with cytoreduction or steroids, the severe consequences of these conditions can be prevented. pERC also noted that the trials had only a short follow-up period and could not provide information on long-term harms. pERC noted that induction therapy is generally administered in-hospital while consolidation therapy is administered on an out-patient basis.

Need: Less toxic therapies and effective treatment options for relapsed/refractory patients

pERC discussed that in the first-line setting, patients with APL are currently treated with ATRA and anthracycline-based chemotherapies, but in the relapsed/refractory setting there are no effective treatment options. pERC noted that APL is an uncommon subtype of acute myelogenous leukemia (AML) accounting for 5% to 8% of AML cases. APL is a very uncommon disease with an estimated age adjusted incidence of 0.073 cases per 100,000 (for the period 1993 – 2007). It was noted that initial remission rates achieved with ATRA are high, ranging from 80% to 100% in some studies. Relapse however occurs in approximately 20% of cases. pERC also noted there are important short-term and long-term toxicities associated with ATRA and these chemotherapies including APL differentiation syndrome, second primary malignancies, cardiomyopathy and myelodysplasia. Therefore, pERC considered that there is a need for treatments with an improved toxicity profile in the first-line setting and an even greater need for effective therapies in the relapsed/refractory setting. pERC also discussed the burden of illness of APL and noted that this is a very uncommon cancer. It was discussed that because only about 20% of patients relapse after first-line therapy, the number of patients to be treated in the relapsed setting would be even smaller than in the first-line setting. pERC also discussed that providing access to arsenic trioxide in the first-line setting could result in fewer relapses, lowering the number of patients requiring treatment in the relapse setting.

PATIENT-BASED VALUES

Values of patients with APL: longer remission and improved quality of life

Input from a patient advocacy group relevant to both the first-line and relapsed/refractory settings indicated that patients with APL are looking for treatment options that provide longer remission rates. pERC also discussed that untreated patients who are diagnosed with APL are treated as an emergency in order to prevent severe consequences and death. However, some patients who relapse after previous treatment may experience a molecular relapse rather than a clinical relapse. pERC considered that based on the event-free survival rates and complete remission rates observed in the arsenic studies included in the pCODR review, arsenic aligns with the patient value of having effective treatments that induce remission. pERC noted that APL affects a younger population ranging from children to adults and noted that the disease and associated treatment has a significant impact on their day-to-day quality of

life.However, none of the first-line or relapsed/refractory studies measured quality of life or functional outcomes. pERC considered this a very important outcome, particularly when the toxicity profile of treatments such as ATRA and anthracycline-based chemotherapies are a concern. Therefore, pERC was limited in its ability to determine how arsenic trioxide aligns with this patient value. However, pERC noted that access to arsenic trioxide could improve quality of life for patients as they could potentially avoid the toxic effects associated with anthracycline-based chemotherapies.

Patient values on treatment: less short-term and long-term toxicity

pERC deliberated upon the alignment of arsenic trioxide with patient values in both the first-line and relapsed/refractory settings. It was noted that patients are seeking treatments that are as effective or more effective than current therapies but that do not have the short-term and long-term side effects associated with current treatments such as ATRA and chemotherapies. pERC noted that patients with APL experience a number of side effects during their treatment, most of which are related to the chemotherapies used as part of their treatment. pERC also discussed that patients have ongoing long term side effects associated with the chemotherapy based treatment such as memory loss, infertility, depression and anxiety, myelodysplastic syndrome, and bone death. These long-term effects of chemotherapy can be debilitating and patients indicated they have a significant impact on their quality of life. pERC noted that all of the studies evaluating arsenic trioxide had a relatively short follow-up period and could not provide information on the long-term toxicities of arsenic trioxide. However, pERC noted that patients who receive arsenic trioxide could potentially avoid the toxic effects associated with anthracycline-based chemotherapies.

pERC noted that patient input provided information from 10 patients, one of whom who had experience with arsenic trioxide. pERC noted that the patient had been unresponsive to initial therapy experienced complete remission after ATO treatment. The patient indicated that the treatment side effects were mild and more easily tolerated than those experienced with current conventional treatment. pERC also discussed the short-term toxicity profile of arsenic trioxide based on the studies included in the pCODR review and considered that arsenic aligned with these patient values of having access to less toxic treatments.

ECONOMIC EVALUATION

Economic model submitted: cost-effectiveness and cost-utility

The pCODR Economic Guidance Panel assessed:

- a cost-effectiveness and cost-utility analysis assessing the use of ATRA plus ATO versus ATRA plus idarubicin in newly diagnosed (first line) patients with acute APL.
- a cost-effectiveness and cost-utility analysis assessing the use of ATO relative to a combination of ATRA plus chemotherapy in patients with refractory or relapsed APL who have relapsed or are refractory to ATRA plus chemotherapy.

Basis of the economic model: clinical and economic inputs

In both the first line and relapsed/refractory setting, costs considered in the main analysis included treatment costs, drug administration costs, cost of salvage therapy, and medical costs during follow-up. The clinical effects in both analyses were based on event-free survival, post-failure survival, the incidence of adverse events, and utilities.

In the first-line setting, the analysis in low to intermediate risk patients was based on the Lo-Coco study and the analysis in high risk patients was based on the Powell study. In the relapsed/refractory setting, the clinical effects for arsenic trioxide were based on the Soignet 2001 study. However, a range of possible estimates was provided by using effects from two additional studies (Soignet 1998 and Lazo 2003)

Drug costs: drug wastage due to few patients with APL but manageable in practice

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

pERC noted that APL is a uncommon disease, therefore, it is very unlikely that more than one patient will be treated at the same time and at the same center, reducing the ability to share any unused drug from single-use ampoules. Therefore, there is potential for wastage of arsenic trioxide. pERC considered that the impact of wastage could likely be reduced in clinical practice, for example, if centres used extended stability for arsenic trioxide and that wastage had only a small impact on the incremental cost effectiveness ratios.

Cost-effectiveness estimates: transparent modeling and acceptable cost-effectiveness

pERC deliberated upon the cost-effectiveness of arsenic trioxide. pERC discussed the pCODR Economic Guidance Panel's (EGP) appraisal of the submitted economic evaluation and noted that they considered the economic model highly transparent and the EGP was able to modify all of the key parameters in the model, which was an advantage. In the first-line setting, pERC discussed that the EGP and the manufacturer's estimates of cost-effectiveness were similar and both were considered acceptable.

In the relapsed/refractory setting, pERC discussed the range of incremental cost-effectiveness ratios (ICER) provided by the pCODR EGP. pERC discussed that the uncertainty in the ICER was primarily due to the uncertainty in the clinical data provided by the single arm studies. Given that the studies included were single-arm studies, the EGP considered modified analyses by varying the survival estimates from other studies examining the use of ATO in the relapsed/refractory study. It was noted that the manufacturer's estimate was within the EGP's range, and the overall range was considered acceptable by pERC. pERC also noted that in the relapsed/refractory setting, the incremental cost effectiveness ratio was based on receiving one cycle of induction and one cycle of consolidation, although in clinical practice, some patients may get two cycles of consolidation therapy.

pERC also discussed that wastage of arsenic trioxide could slightly increase the ICERs in both the first-line and relapsed/refractory settings, but that the impact of wastage could likely be reduced in clinical practice, for example, if centres used extended stability for arsenic trioxide. Therefore, pERC concluded that at the submitted price, arsenic trioxide is cost-effective in both the first-line and relapsed/refractory settings.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: small budget impact, retreatment with ATO reasonable in relapsed patients

pERC discussed factors affecting the feasibility of implementing a funding recommendation for arsenic trioxide. pERC discussed input from pCODR's Provincial Advisory Group on the use of arsenic trioxide in children. It was noted that some studies in the systematic review allowed for the inclusion of children. Despite the small number of children in these studies, pERC considered this was reasonable for an uncommon disease such as APL and that the underlying pathogenesis of APL is similar in adults and children. Therefore, pERC considered that the results were generalizable to a pediatric population. pERC also discussed that most studies had an upper age limit for enrollment. However, pERC considered that this was likely done to prevent exposure of older adults to the toxicities associated with aggressive chemotherapy in the comparator arms and that use of arsenic trioxide, which does not have these toxicities, would be reasonable in an older population.

pERC also discussed the potential impact of arsenic trioxide on current treatment algorithms. Amongst studies conducted in the relapsed setting, at least one of the studies (Wang 2004) included patients who had received arsenic trioxide as prior treatment in the first-line setting. pERC discussed that currently some patients could be receiving arsenic trioxide re-treatment in the relapsed setting if they had received arsenic trioxide as a first-line treatment through special access programs and that this practice would likely become more common as arsenic trioxide becomes more accessible. Therefore, pERC agreed with the pCODR Clinical Guidance Panel that re-challenge with arsenic trioxide in patients who relapse

following completion of first-line therapy with arsenic trioxide would be reasonable from a clinical perspective.

pERC discussed the potential budget impact of arsenic trioxide and noted that the number of relapsed APL patients is low and that the budget impact would, therefore, likely be small. However, it was noted that APL is an uncommon disease and it is very unlikely that more than one patient would be treated at the same time at the same centre, thus leading to the potential wastage of unused ampoules during a given treatment course. pERC also considered that the impact of wastage could likely be reduced in clinical practice, for example, if centres used extended stability for arsenic.

pERC noted that induction therapy is generally administered in-hospital while consolidation therapy is administered on an out-patient basis. pERC discussed the different dosing regimens that were evaluated and noted that treatment schedules were evaluated in which patients received consolidation treatment 5 days per week (e.g. Lo-Coco 2013), rather than consecutively. Therefore, there is an evidence base for this treatment schedule, which is an enabler to outpatient administration compared with daily administration (i.e. 7 days per week).

pERC also discussed that although PAG had identified the potential for indication creep into the treatment of patients with myelodysplastic syndrome, this was unlikely to occur in clinical practice as there is no evidence for the use of arsenic trioxide in these patients.

DRUG AND CONDITION INFORMATION

Drug Information	• Mechanism of action unclear • 10 mg single-use ampoule • During induction, 0.15 mg/kg/day until complete remission or a maximum of 60 doses. During consolidation, 0.15 mg/kg/day for 5 days per week for four weeks every 8 weeks (for a total of 90 treatments).
Cancer Treated	• Acute promyelocytic leukemia (APL) • First-line and relapsed or refractory settings
Burden of Illness	• Uncommon disease with an incidence of 0.073 cases per 100,000 for the period 1993 - 2007 • Complete remission rates up to 80% in first-line setting • Relapse occurs in approximately 20% of cases
Current Standard Treatment	• First line: ATRA plus anthracycline-based chemotherapies • Relapsed/refractory: ATRA and anthracycline-based chemotherapy for re-induction followed by further chemotherapy consolidation with or without stem cell transplantation.
Limitations of Current Therapy	• Short-term toxicities associated with aggressive chemotherapies and ATRA • Long-term adverse effects, e.g. second cancers, cardiomyopathy and myelodysplasia • Lack of effective options in relapsed/refractory setting

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee (pERC)

Recommendations are made by the pCODR Expert Review Committee following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Anthony Fields, Oncologist (Chair)
Dr. Maureen Trudeau, Oncologist (Vice-Chair)
Dr. Chaim Bell, Economist
Dr. Scott Berry, Oncologist
Bryson Brown, Patient Member
Dr. Matthew Cheung, Oncologist;
Mario de Lemos, Pharmacist
Dr. Sunil Desai, Oncologist
Mike Doyle, Economist
Dr. Bill Evans, Oncologist
Dr. Allan Grill, Family Physician
Dr. Paul Hoskins, Oncologist
Danica Wasney, Pharmacist
Carole McMahon, Patient Member Alternate
Jo Nanson, Patient Member
Dr. Peter Venner, Oncologist
Dr. Tallal Younis, Oncologist

All members participated in deliberations and voting on the initial recommendation except:

- Dr. Scott Berry who was not present for the meeting
- Dr. Matthew Cheung and Dr. Sunil Desai who were excluded from voting due to a conflict of interest
- Carole McMahon who did not vote due to her role as a patient member alternate

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of arsenic trioxide (Trisenox) for acute promyelocytic leukemia, through their declarations, two members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, both were excluded from voting.

Information sources used

The pCODR Expert Review Committee is provided with a *pCODR Clinical Guidance Report* and a *pCODR Economic Guidance Report*, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions to inform their deliberations. pCODR guidance reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR guidance reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There is no non-disclosable information in this recommendation document.

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