Blinatumomab (PX0367)
FMEC Responses to Questions from the Drug Programs

Response Summary

Drug Program Implementation Questions	Clinical expert response	FMEC response
Relevant comparators		
Issues have been identified with the choice of comparator in the submitted trials. The study compared addition of blinatumomab replaced block 3, and then chemotherapy followed by 2 x blinatumomab infusions intercalated with chemotherapy prior to maintenance vs. standard therapy (vincristine, dexamethasone, pegaspargase, mitoxantrone, and risk-based intrathecal chemotherapy including two intensive chemotherapy blocks followed by two continuation cycles and maintenance chemotherapy.	The clinical experts agreed that this remains an appropriate comparator for patients in the low-risk population, and that the blinatumomab regimen mentioned is currently used in most Canadian institutions. The experts also noted that the current standard chemotherapy regimen is highly intensive and associated with a higher risk of treatment-related mortality. They suggested that it may be advisable to de-intensify the chemotherapy for adolescents and young adults (AYA), as these patients tend to experience greater toxicity and poorer outcomes. This is especially relevant for those transitioning to immunotherapy with blinatumomab.	FMEC agrees with experts
Considerations for initiation of therapy		
Would patients with CNS disease be eligible for treatment?	The experts indicated that patients with CNS disease would be eligible for treatment with blinatumomab if they have evidence of combined systemic and bone marrow disease. However, one expert also noted that as per AALL 1331, patients with isolated CNS relapse, a subset for which the	FMEC agrees with experts Refer to the initiation condition as outlined in Table 2 of the recommendation report.

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	blinatumomab-containing arm was demonstrated to have inferior outcomes compared to the standard treatment arm.	
Considerations for prescribing of therapy		
Blinatumomab is administered as a 28-day infusion requiring specialized pumps and training of staff. Jurisdictions have implemented blinatumomab for other indications/criteria and have experience. Patients may need to travel to facilities which are equipped to prepare and support patients on these pumps. It is anticipated that patients will receive additional cycles/doses of blinatumomab in this setting vs. Second line or later relapse setting?	The experts noted that in the first-relapse setting, blinatumomab can be administered with curative intent, without necessarily proceeding to HSCT. However, for patients in second relapse or beyond, the standard of care for curative therapy remains HSCT or CAR T-cell therapy. Since the standard of care differs between these settings, direct comparisons are challenging due to the distinct nature of each situation.	FMEC agrees with experts. FMEC also notes that different blinatumomab dosage regimens have been evaluated in the included studies. In the Locatelli study, high-risk patients received one cycle of blinatumomab administered as a continuous infusion of 15mg/m^2 once daily over 28 days. In the COG ALL 1331 study, patients received up to 3 cycles of blinatumomab
Generalizability		
Patients with Down syndrome, Philadelphia chromosome–positive (Ph-positive) ALL, prior HSCT, or prior blinatumomab treatment were excluded from the trial. Patients with Burkitt Leukemia/Lymphoma, T-ALL and B-ALL were not eligible. In second line or later, patients who failed HSCT were eligible. Would this be applicable for patients with 1st or later relater relapse as well? Would Ph-positive patients be considered eligible recognizing that in practice, all relapsed/refractory patients are treated the same?	The experts indicated that these patients should be considered eligible for blinatumomab, despite their exclusion from clinical trials for various reasons. For example, patients with Down syndrome experience higher toxicity from intensive chemotherapy, potentially skewing trial results. However, these factors should not preclude them from receiving blinatumomab. Only patients who have lost CD19 expression are unlikely to benefit from the therapy. The experts also indicated that patients who have previously	FMEC cannot comment on the use of blinatumomab in these subpopulations as they are out of scope for this review. There is also a lack of evidence for blinatumomab in these subpopulations.

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	failed HSCT and are in first relapse should be eligible for blinatumomab. Additionally, they emphasized that Ph-positive patients should be eligible for the treatment, noting that in the adult population, where Ph-positive cases are more common, blinatumomab is considered a standard of care. Biologically, there is no reason to believe Ph-positive patients would respond differently.	
Funding algorithm (oncology only)		
This is a complex therapeutic space with multiple lines of therapy, subpopulations, or competing products	N/A	This is a comment from the drug plans to inform FMEC deliberations.
Blinatumomab may change place in therapy of drugs reimbursed in subsequent lines.	N/A	This is a comment from the drug plans to inform FMEC deliberations.
Care provision issues		
Drug is initiated in the inpatient setting.	N/A	This is a comment from the drug plans to inform FMEC deliberations.
Treatment of tumor lysis syndrome, Cytokine release syndrome and neurological toxicities may occur upon initiation and will be monitored and managed in the hospital.	N/A	This is a comment from the drug plans to inform FMEC deliberations.
System and economic issues		
There is concern about the budget impact and sustainability of blinatumomab. Will additional doses of blinatumomab be required in this setting compared to the current funded blinatumomab for patients in second relapse or later? A cost effectiveness utility analysis may be useful to assess the ICER as patients who are in first relapse or	N/A	This is a comment from the drug plans to inform FMEC deliberations.

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later would be fitter than those in second relapse.		
Blinatumomab has gone through confidential pricing negotiations for multiple indications.	N/A	This is a comment from the drug plans to inform FMEC deliberations.

ALL = acute lymphoblastic leukemia; B-ALL = B-cell acute lymphoblastic leukemia; CAR T-cell therapy = chimeric antigen receptor cell therapy; CNS = central nervous system; FMEC = formulary management committee; HSCT = hematopoietic stem cell transplant; ICER = incremental cost-effectiveness ratio; N/A = not applicable; T-ALL = T-cell acute lymphoblastic leukaemia