

I.1	Cancer medicines for children – anaplastic large cell lymphoma – EMLc
<p>Draft recommendation</p>	<p><input checked="" type="checkbox"/> Recommended</p> <p><input checked="" type="checkbox"/> Not recommended</p> <p>Justification:</p> <p>Cyclophosphamide 500mg powder for injection, cytarabine 25mg/ml, dexamethasone tablets, doxorubicin 2mg/ml, etoposide 20mg/ml, ifosfamide powder for injection (1000mg), methotrexate 25mg/ml and prednisolone 25mg powder for injection are standard of care and essential in the first-line treatment of ALCL in children and adolescents. Vinblastine 1mg/ml is essential in the treatment of relapsed/refractory disease. These compounds are already included in the WHO EMLc 2021 for other indications.</p> <p>It is therefore recommended that a new indication be included for all these compounds with Cyclophosphamide, cytarabine 25mg/ml, dexamethasone tablets, doxorubicin 2mg/ml, etoposide 20mg/ml, ifosfamide powder for injection (1000mg), methotrexate 25mg/ml and prednisolone 25mg powder for injection as first line therapy and vinblastine 1mg/ml for the treatment of relapsed/refractory disease.</p> <p>Insufficient evidence and toxicity concerns for crizotinib in the treatment of children and adolescents with refractory/relapsed ALCL exists, and therefore it is not recommended for inclusion at this time.</p>
<p>Does the proposed medicine address a relevant public health need?</p>	<p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments: Non-Hodgkin lymphoma (NHL) is the fourth most common type of cancer in children and adolescents with an incidence of about 0.7 – 1.5 per 100,000 per year in Europe. 10-15% of these are ALCL.</p> <p>It has been reported that over 80% of paediatric cancers globally occur in children who live in low and middle income countries (LMICs); it is estimated that 90% of children diagnosed with NHL live in LMIC.¹ Anaplastic large cell lymphoma (ALCL) accounts for 10- 20% of pediatric and adolescent non-Hodgkin lymphomas (NHLs).^{2 3}</p>
<p>Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication?</p> <p>(this may be evidence included in the application, and/or additional evidence identified during the review process)</p>	<p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments: These medicines are already included in the EML and EMLc for other indications.</p> <p>Crizotinib is a new recommendation and there is insufficient indication of efficacy/effectiveness currently.</p>

¹ Gross TG, Biondi A. Paediatric non-Hodgkin lymphoma in low and middle income countries. Br J Haematol. 2016 May;173(4):651-4. doi: 10.1111/bjh.14030. Epub 2016 Apr 20. PMID: 27098084; PMCID: PMC4862913

² Burkhardt, B.; Zimmermann, M.; Oschlies, I.; Niggli, F.; Mann, G.; Parwaresch, R.; Riehm, H.; Schrappe, M.; Reiter, A.; The BFM Group. The impact of age and gender on biology, clinical features and treatment outcome of non-Hodgkin lymphoma in childhood and adolescence. Br. J. Haematol. 2005, 131, 39–49

³ Aladily TN, Khader M, Bustami N, Bazzeh F. Anaplastic large cell lymphoma, ALK-positive in very young children: A long-term follow-up of two cases and a review of the literature. Malays J Pathol. 2022 Dec;44(3):517-521. PMID: 36591719.

<p>Does adequate evidence exist for the safety/harms associated with the proposed medicine?</p> <p>(this may be evidence included in the application, and/or additional evidence identified during the review process)</p>	<p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments: The medicines recommended for the new indication are already in the WHO EML and EMLc.</p> <p>However, toxicity concerns exist for Crizotinib . Although crizotinib induces remissions and extends the lives of patients, there have been reports of emerging resistance to Crizotinib therapy. Toxicity has been reported as well.⁴</p>
<p>Are there any adverse effects of concern, or that may require special monitoring?</p>	<p><input type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input checked="" type="checkbox"/> Not applicable</p> <p>Comments: For crizotinib side effects of grade III/IV occurred, including elevated transaminase levels, diarrhea, and prolonged QT intervals, in 8% patients, with dose reduction in six patients (15.8%).⁵</p>
<p>Are there any special requirements for the safe, effective and appropriate use of the medicines?</p> <p>(e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)</p>	<p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments: Some of the medications are IV/IMI administered and therefore require skilled personnel for administration. Diagnostic capabilities are required as are skills in identifying the condition and managing side effects and toxicities.</p>
<p>Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?</p>	<p><input type="checkbox"/> Yes</p> <p><input checked="" type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments: These medicines are available at affordable prices globally. Generics do exist, so competitive pricing exists.</p>
<p>Are there any issues regarding the registration of the medicine by national regulatory authorities?</p> <p>(e.g. accelerated approval, lack of regulatory approval, off-label indication)</p>	<p><input type="checkbox"/> Yes</p> <p><input checked="" type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments: These compounds are registered in many NRAs globally</p>

⁴ Sahu A, Prabhash K, Noronha V, Joshi A, Desai S. Crizotinib: A comprehensive review. South Asian J Cancer. 2013 Apr;2(2):91-7. doi: 10.4103/2278-330X.110506. PMID: 24455567; PMCID: PMC3876666

⁵ Mohieldin A, Rasmy A, Ashour M, Al-Nassar M, Ali RH, El-Enezi FG. Efficacy and safety of crizotinib in patients with anaplastic lymphoma kinase-positive advanced-stage non-small-cell lung cancer. Cancer Manag Res. 2018 Nov 29;10:6555-6561. doi: 10.2147/CMAR.S173084. PMID: 30555260; PMCID: PMC6278708.

<p>Is the proposed medicine recommended for use in a current WHO guideline?</p> <p>(refer to: https://www.who.int/publications/who-guidelines)</p>	<p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>Cyclophosphamide Powder for injection: 500 mg; 1 g; 2 g in vial; Tablet: 25 mg; 50 mg.: Acute lymphoblastic leukaemia, Burkitt lymphoma, Diffuse large B-cell lymphoma, Ewing sarcoma, Hodgkin lymphoma, Low-grade glioma, Nephroblastoma (Wilms tumour), Rhabdomyosarcoma</p> <p>Cytarabine Powder for injection: 100 mg in vial: Acute lymphoblastic leukaemia, Acute myeloid leukaemia, Acute promyelocytic leukaemia, Burkitt lymphoma</p> <p>Dexamethasone is found under antiemetic medicines, medicines for other symptoms common in palliative care, antiallergics and medicines used in anaphylaxis, as well as hormones and antihormones as injection; Oral liquid and solid oral dosage form.</p> <p>Doxorubicin Powder for injection: 10 mg; 50 mg (hydrochloride) in vial: Acute lymphoblastic leukaemia, Burkitt lymphoma, Diffuse large B-cell lymphoma, Ewing sarcoma, Hodgkin lymphoma, Kaposi sarcoma, Nephroblastoma (Wilms tumour), Osteosarcoma</p> <p>Etoposide Capsule: 50 mg; 100 mg; Injection: 20 mg/mL in 5 mL ampoule: Acute lymphoblastic leukaemia, Acute myeloid leukaemia, Burkitt lymphoma, Ewing sarcoma, Hodgkin lymphoma, Nephroblastoma (Wilms tumour), Osteosarcoma, Ovarian germ cell tumours, Retinoblastoma, Testicular germ cell tumours</p> <p>Ifosfamide Powder for injection: 500 mg; 1 g; 2 g in vial: Burkitt lymphoma, Ewing sarcoma, Nephroblastoma (Wilms tumour), Osteosarcoma, Ovarian germ cell tumours, Rhabdomyosarcoma, Testicular germ cell tumours</p> <p>Methotrexate Powder for injection: 50 mg (as sodium salt) in vial; Tablet: 2.5 mg (as sodium salt): Acute lymphoblastic leukaemia; Acute promyelocytic leukaemia; Burkitt lymphoma; Osteosarcoma</p> <p>Prednisolone Oral liquid: 5 mg/mL, Tablet: 5 mg; 25 mg: Acute lymphoblastic leukaemia; Burkitt lymphoma, Diffuse large B-cell lymphoma, Hodgkin lymphoma</p> <p>Vinblastine Injection: 10 mg/10 mL (sulfate) in vial, Powder for injection: 10 mg (sulfate) in vial: Hodgkin lymphoma, Low-grade glioma, Ovarian germ cell tumours, Testicular germ cell tumours</p>
--	---