




		EMLc	ATC codes: L01AA06
Indication	Malignant neoplasms of kidney, except renal pelvis	ICD11 code: 2D40.Z	
INN	Ifosfamide		
Medicine type	Chemical agent		
List type	Complementary		
Formulations	Parenteral > General injections > IV: 500 mg in vial powder for injection ; 1 g in vial powder for injection ; 2 g in vial powder for injection		
EML status history	First added in 2021 (TRS 1035)		
Sex	All		
Age	Also recommended for children		
Therapeutic alternatives	The recommendation is for this specific medicine		
Patent information	Patents have expired in most jurisdictions Read more about patents . 		
Tags	Cancer		
Wikipedia	Ifosfamide 		
DrugBank	Ifosfamide 		

Expert Committee recommendation

The Expert Committee noted that the incidence of paediatric tumours has been steadily increasing over the past decades with the largest increases reported in youngest children. The Expert Committee recommended the extension of the current listings on the complementary list of the EMLc of the medicines outlined in the following table for the indications specified. Noting that these paediatric cancers also affect older children and adolescents, the Committee also recommended extending the listings for these medicines on the EML. Medicine: (Indication(s)) Carboplatin: (Nephroblastoma, ovarian and testicular germ cell tumours) Cyclophosphamide: (Nephroblastoma) Dactinomycin: (Ewing sarcoma) Dexamethasone: (Burkitt lymphoma) Etoposide: (Acute myeloid leukaemia, nephroblastoma, osteosarcoma) Hydrocortisone: (Burkitt lymphoma) Ifosfamide: (Burkitt lymphoma, nephroblastoma) Imatinib: (Acute lymphoblastic leukaemia) Irinotecan: (Nephroblastoma, rhabdomyosarcoma) Methotrexate: (Burkitt lymphoma) Methylprednisolone: (Burkitt lymphoma) The Committee noted that administration of intravenous cyclophosphamide or ifosfamide required the use of the accompanying medicine mesna to prevent haemorrhagic cystitis commonly associated with these treatments. The Committee therefore also recommended the extension of the current listing for mesna on the EML and EMLc to include the indications of nephroblastoma and Burkitt lymphoma.

Background

The proposed medicines are all included on the EMLc for other cancer indications.

Public health relevance

Cancer is a leading cause of death in children globally; the most common cancer types in children are leukaemias, lymphomas and central nervous system tumours (1). Childhood cancers generally cannot be prevented or screened for, so improving outcomes for

children with cancer relies on early and accurate diagnosis and access to effective treatments. In 2018, WHO launched the Global Initiative for Childhood Cancer, to provide leadership and technical assistance to Member States to build and sustain high-quality childhood cancer programmes. The goal of this initiative is to achieve at least 60% survival for all children with cancer globally by 2030 (2).

Benefits

Cancer in children and adolescents is almost exclusively treated according to national and international treatment protocols. This is the case for first treatment and relapsed and refractory disease. Treatment regimens are devised by clinical experts from relevant tumour groups and are further developments of previous regimens. Often these treatment protocols consist of the standard arm that has proven to be effective based on previous experimental trials. All medicines proposed in this application are part of international treatment regimens and are considered the standard of care. Acute myeloid leukaemia – etoposide Etoposide is included in multiple trial regimens as standard therapy for children with acute myeloid leukaemia, including the AML-BFM 2012 (3), NOPHO-DBH AML 2012 (4) and ML DS 2006 (5) trials. Nephroblastoma – carboplatin, cyclophosphamide, etoposide, ifosfamide, irinotecan Carboplatin, cyclophosphamide, etoposide, ifosfamide and irinotecan are included as chemotherapy interventions along with dactinomycin, doxorubicin, melphalan and vincristine in the SIOP 2001/GPOH (6) and Umbrella SIOP-RTSG 2016 (7) trial regimens for nephroblastoma (Wilms tumour). Acute lymphoblastic leukaemia – imatinib Imatinib is included in the ALLTogether trial regimen for children and young adults with acute lymphoblastic leukaemia (8) and the EsPhALL trial regimen for children with Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukaemia (9). Ewing sarcoma – dactinomycin Dactinomycin is included in many trial regimens for Ewing sarcoma, including EICESS-92 (10), Euro-Ewing 2012 (11,12) and Euro-Ewing 99 (13,14) trials. Ovarian and testicular germ cell tumours – carboplatin Carboplatin is included in the MAKEI-V regimen for malignant extracranial germ cell tumours (15), and is recommended in chemotherapy regimens for extracranial germ cell tumours in children and adolescents in guidelines issued by the Children's Cancer and Leukaemia Group in the United Kingdom of Great Britain and Northern Ireland (16). Burkitt lymphoma – dexamethasone, hydrocortisone, ifosfamide, methylprednisolone, methotrexate Dexamethasone, ifosfamide and methotrexate are included in the LBL 2018 regimen for Burkitt lymphoma (17). Hydrocortisone, methylprednisolone and methotrexate are included in the Inter-B-NHL Ritux 2010 regimen (18,19). Osteosarcoma – etoposide Etoposide is included in the French OS2006 regimen for osteosarcoma (20,21). Rhabdomyosarcoma – irinotecan Irinotecan is included in the EpSSG FaR-RMS (22) and the VIT-0910 regimens for frontline or relapsed or refractory rhabdomyosarcoma (23,24).

Harms

Chemotherapy is associated with serious adverse events in the acute setting and also in the long term in cancer survivors; it therefore requires close monitoring (25–27). All proposed medicines in this application are already included on the EMLc. Their safety profiles are well known as a result of long-standing experience with their use.

Cost / cost effectiveness

Not reported in the application.

WHO guidelines

WHO guidelines for the treatment of paediatric cancer are not available. Burkitt lymphoma and nephroblastoma are among the six tracer cancers in the WHO Global Initiative for Childhood Cancer.

Availability

The proposed medicines are already included on the EMLc and are available in branded and generic forms.

Other considerations

The EML Cancer Medicines Working Group advised that it supported expansion of the listings on the EMLc for the proposed cancer medicines for the proposed new indications. These medicines are all used in standard, multimodal chemotherapy protocols for the proposed indications. Expanding the EMLc indications for these medicines would support the goals of WHO Global Paediatric

Cancer initiative and contribute towards the achievement of the best possible cancer care for children. The Working Group acknowledged that the availability of clinical evidence in the paediatric context was limited but considered that obtaining the usual level of evidence required for EML listings was unlikely. In this case, efficacy and safety could be accepted based on extrapolation of the well known benefits and harms from use of these medicines in adults, for other indications in children and as part of standard cancer care in children.

1. Steliarova-Foucher E, Colombet M, Ries LAG, Moreno F, Dolya A, Bray F, et al. International incidence of childhood cancer, 2001–10: a population-based registry study. *Lancet Oncol.* 2017;18(6):719–31.
2. WHO Global Initiative for Childhood Cancer: an overview. Geneva: World Health Organization; 2020 (<https://www.who.int/publications/m/item/global-initiative-for-childhood-cancer>, accessed 18 May 2021).
3. AML-BFM-2012 – Clinical trial for the treatment of acute myeloid leukemia in children and adolescents. Amsterdam: EU Clinical Trials Register; 2014 (EudraCT number 2013-000018-39; <https://www.clinicaltrialsregister.eu/ctr-search/trial/2013-000018-39/DE>, accessed 18 May 2021).
4. NOPHO-DBH AML 2012 protocol. Research study for treatment of children and adolescents with acute myeloid leukaemia 0–18 years. Bethesda, MD: U.S. National Library of Medicine; 2013 (ClinicalTrials.gov Identifier: NCT01828489; <https://www.clinicaltrials.gov/ct2/show/NCT01828489>, accessed 18 May 2021).
5. Phase III clinical trial for CPX-351 in myeloid leukemia in children with down syndrome 2018. Amsterdam: EU Clinical Trials Register; 2020 (EudraCT number 2018-002988-25; <https://www.clinicaltrialsregister.eu/ctr-search/trial/2018-002988-25/DE>, accessed 18 May 2021).
6. Chemotherapy before and after surgery in treating children with Wilm’s tumor. Bethesda, MD: U.S. National Library of Medicine; 2003 (ClinicalTrials.gov Identifier: NCT00047138; <https://www.clinicaltrials.gov/ct2/show/NCT00047138>, accessed 18 May 2021).
7. UMBRELLA protocol SIOP-RTSG 2016 – Integrated research and guidelines for standardized diagnostics and therapy of kidney tumours in children, adolescents and young adults. Cologne: Deutsches Register Klinischer Studien; 2017 (DRKS-ID: DRKS00011208; https://www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00011208, accessed 18 May 2021).
8. A treatment study protocol of the ALLtogether Consortium for Children and Young Adults (1–45 Years of Age) With Newly Diagnosed Acute Lymphoblastic Leukaemia (ALL): a pilot study. Bethesda, MD: U.S. National Library of Medicine; 2019 (ClinicalTrials.gov Identifier: NCT03911128; <https://clinicaltrials.gov/ct2/show/NCT03911128>, accessed 18 May 2021).
9. Safety and efficacy of imatinib added to chemotherapy in treatment of Ph+ acute lymphoblastic leukemia in children (ESPHALL). Bethesda, MD: U.S. National Library of Medicine; 2006 (ClinicalTrials.gov Identifier: NCT00287105; <https://clinicaltrials.gov/ct2/show/NCT00287105>, accessed 18 May 2021).
10. Paulussen M, Craft AW, Lewis I, Hackshaw A, Douglas C, Dunst J, et al. Results of the EICESS-92 study: two randomized trials of Ewing’s sarcoma treatment—cyclophosphamide compared with ifosfamide in standard-risk patients and assessment of benefit of etoposide added to standard treatment in high-risk patients. *J Clin Oncol.* 2008;26(27):4385–93.
11. Combination chemotherapy with or without peripheral stem cell transplantation, radiation therapy, and/or surgery in treating patients with Ewing’s sarcoma. Bethesda, MD: U.S. National Library of Medicine; 2003 (ClinicalTrials.gov Identifier: NCT00020566; <https://clinicaltrials.gov/ct2/show/NCT00020566>, accessed 18 May 2021).
12. Brennan B, Kirton L, Marec-Berard P, Martin-Broto JM, Gelderblom H, Gaspar N, et al. Comparison of two chemotherapy regimens in Ewing sarcoma (ES): overall and subgroup results of the Euro Ewing 2012 randomized trial (EE2012). *J Clin Oncol.* 2020;38(15 Suppl):11500.
13. Le Deley MC, Paulussen M, Lewis I, Brennan B, Ranft A, Whelan J, et al. Cyclophosphamide compared with ifosfamide in consolidation treatment of standard-risk Ewing sarcoma: results of the randomized noninferiority Euro-EWING99-R1 trial. *J Clin Oncol.* 2014;32(23):2440–8.
14. Whelan J, Le Deley MC, Dirksen U, Le Teuff G, Brennan B, Gaspar N, et al. High-dose chemotherapy and blood autologous stem-cell rescue compared with standard chemotherapy in localized high-risk Ewing sarcoma: results of Euro-E.W.I.N.G.99 and Ewing-2008. *J Clin Oncol.* 2018;36(31):Jco2018782516.
15. Multicentre prospective trial for extracranial germ cell tumours including a randomized comparison of carboplatin and cisplatin. Amsterdam: EU Clinical Trials Register; 2019 (EudraCT number 2016-001784-36; <https://www.clinicaltrialsregister.eu/ctr-search/trial/2016-001784-36/DE>, accessed 18 May 2021).
16. Interim guidelines for the treatment of extracranial germ cell tumours in children and adolescents. Leicester: Children’s Cancer and Leukaemia Group; 2018 ([https://www.cclg.org.uk/write/MediaUploads/Member%20area/Treatment%20guidelines/614_Extra cranial_GCT_Guidance_updated_June_2018.pdf](https://www.cclg.org.uk/write/MediaUploads/Member%20area/Treatment%20guidelines/614_Extra%20cranial_GCT_Guidance_updated_June_2018.pdf), accessed 18 May 2021).
17. International cooperative treatment protocol for children and adolescents with lymphoblastic lymphoma (LBL 2018). Bethesda, MD: U.S. National Library of Medicine; 2019 (ClinicalTrials.gov Identifier: NCT04043494; <https://www.clinicaltrials.gov/ct2/show/NCT04043494>, accessed 18 May 2021).
18. Minard-Colin V, Aupérin A, Pilon M, Burke GAA, Barkauskas DA, Wheatley K, et al. Rituximab for high-risk, mature b-cell non-Hodgkin’s lymphoma in children. *N Engl J Med.* 2020;382(23):2207–19.
19. Intergroup trial for children or adolescents with B-cell NHL Or B-AL: evaluation of rituximab efficacy and safety in high risk patients Amsterdam: EU Clinical Trials Register; 2011 (EudraCT number 2010-019224-31; <https://www.clinicaltrialsregister.eu/ctr-search/trial/2010-019224-31/NL>, accessed 18 May 2021).
20. Combined chemotherapy with or without zoledronic acid for patients with osteosarcoma (OS2006). Bethesda, MD: U.S. National Library of Medicine; 2007 (ClinicalTrials.gov Identifier: NCT00470223; <https://www.clinicaltrials.gov/ct2/show/NCT00470223>, accessed 18 May 2021).
21. Gaspar N, O’cean BV, Pacquement H, Bompas E, Bouvier C, Brisse HJ, et al. Results of methotrexate-etoposide-ifosfamide based regimen (M-EI) in osteosarcoma patients included in the French OS2006/sarcome-09 study. *Eur J Cancer.* 2018;88:57–66.
22. FaR-RMS: an overarching study for children and adults with Frontline and Relapsed RhabdoMyoSarcoma. Amsterdam: EU Clinical Trials Register; 2020 (EudraCT number 2018-000515-24; <https://www.clinicaltrialsregister.eu/ctr-search/trial/2018-000515-24/NL>, accessed 18 May 2021).
23. Defachelles AS, Bogart E, Casanova M, Merks H, Bisogno G, Calareso G, et al. Randomized phase 2 trial of the combination of vincristine and irinotecan with or without temozolomide, in children and adults with refractory or relapsed rhabdomyosarcoma (RMS). *J Clin Oncol.* 2019;37(15 Suppl):10000.
24. Vincristine and irinotecan with or without temozolomide in children and adults with refractory/relapsed rhabdomyosarcoma (VIT-0910). Bethesda, MD: U.S. National Library of Medicine; 2011 (ClinicalTrials.gov Identifier: NCT01355445; <https://www.clinicaltrials.gov/ct2/show/NCT01355445>, accessed 18 May 2021).
25. Institute of Medicine, National Research Council. Hewitt M, Weiner SL, Simone JV, editors. Childhood cancer survivorship: improving care and quality of life. Washington, DC: The National Academies Press; 2003:224.
26. Landier W, Bhatia S, Eshelman DA, Forte KJ, Sweeney T, Hester AL, et al. Development of risk-based guidelines for pediatric cancer survivors: the Children’s Oncology Group long-term follow-up guidelines from the Children’s Oncology Group Late Effects Committee and Nursing Discipline. *J Clin Oncol.* 2004;22(24):4979–90.
27. Wasilewski-Masker K, Mertens AC, Patterson B, Meacham LR. Severity of health conditions identified in a pediatric cancer survivor program. *Pediatr Blood Cancer.* 2010;54(7):976–82.

