The European Society for Paediatric Oncology (SIOP Europe)

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Application for New Allocation of already Approved Medicines and Indications on the WHO cEML 2021

2021 WHO Expert Committee on the Selection and Use of Essential Medicines

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1. Summary statement of the proposal for inclusion.

Following the Joint Action on Rare Cancers (JARC, 724161, EU Health Programme) Conclusions, the European Society for Paediatric Oncology (SIOP Europe) has initiated a pan-European project to develop a list of anticancer medicines that are essential to treat children and adolescents with cancer in Europe by mobilising the pan-European community of clinicians, researchers, and parents to take part in the project. Activities were led by a leading clinicians and researchers from the SIOP Europe Board, Young SIOP Europe members, senior mentors from European Clinical Trial Groups, and parent representatives from CCI-Europe. Synergies are ensured with the European Reference Network for Paediatric Cancers (ERN PaedCan) and the WHO Global Initiative for Childhood Cancer. A total of 54 SIOP Europe members (Young SIOP Europe members and their mentors), divided into 16 tumour groups, worked on this project.

Identified anticancer medicines cover all paediatric malignancies and derive from a systematic collection and screen of all academic national and international European standard treatment protocols, registries and regimens. "Anticancer medicines in the standard arm of upfront and relapse treatment protocols were defined as "essential" for the purpose of this project. Additionally, also supportive care medicines closely linked to essential anticancer medicines were included. In other words, all anticancer medicines which are standard of care are considered "*essential"*.

For all identified medicines, which were not on the WHO cEML 2017 list, a thorough literature search was performed by the Young SIOPE members in collaboration with the senior experts within the tumour groups to collect data on the efficacy and relevance of the listed medicines. Last, a designated reviewer, belonging to the respective tumour group and being an expert in the field, was assigned to edit and approve the suggested list.

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Reviewing this list, we defined three categories of medicines and identified malignancies/indications not considered on the current WHO cEML: 1.Medicines already listed on the cEML 2019 for a certain indication, but not for the indication identified and proposed by SIOPE. 2. Medicines not yet listed on the cEML 2019 for indications already existing on the cEML 2019. 3. Medicines and their belonging indication not yet listed on the cEML 2019. According to these categories, several medicines have been identified, which are already listed on the cEML 2019 for a certain indication/malignancy, however not for all indications for which they are considered to be standard of care (first category). In this document we will provide a summary of the collected data that support adding additional indications for these specific medicines from the first category.

The following table summarises these medicines, their WHO-approved indication and the additional indication proposed by SIOPE.

Medicine	**WHO indication in EMLc 2019**	**Additional indication according to SIOPE**
Carboplatin	Osteosarcoma Retinoblastoma	Ovarian and Testicular Germ Cell Tumor Nephroblastoma
Cyclophosphamide	Rhabdomyosarcoma Ewing sarcoma Acute lymphoblastic leukaemia Burkitt lymphoma Hodgkin lymphoma Diffuse large B-cell lymphoma	Nephroblastoma
Dactinomycin	Rhabdomyosarcoma Nephroblastoma	Ewing sarcoma
Dexamethason	Acute lymphoblastic leukaemia	Burkitt lymphoma
Etoposide	Retinoblastoma Ewing sarcoma Acute lymphoblastic leukaemia Burkitt lymphoma Hodgkin lymphoma Testicular germ cell tumours Ovarian germ cell tumours	Acute myeloid leukaemia Osteosarcoma Nephroblastoma
Hydrocortisone	Acute lymphoblastic leukaemia	Burkitt lymphoma
Ifosfamide	Osteosarcoma Rhabdomyosarcoma	Burkitt lymphoma Nephroblastoma

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	Ewing sarcoma Testicular germ cell tumours Ovarian germ cell tumours	
Imatinib	Chronic myeloid leukaemia Gastrointestinal stromal tumour	Acute lymphoblastic leukaemia
Irinotecan	Metastatic colorectal cancer	Nephroblastoma, Rhabdomyosarcoma
Methotrexate	Osteosarcoma Acute lymphoblastic leukaemia Acute promyelocytic leukaemia.	Burkitt lymphoma
Methylprednisolone	Acute lymphoblastic leukaemia	Burkitt lymphoma

As the team of the SIOP Europe Essential Medicines Project, we propose to the WHO to add all the listed medicines to the indications which are present on the WHO cEML already.

All these compounds are longstanding and well-known medicines, and most importantly the standard of care for the above mentioned indications. Please find below (point 7) the corresponding names of the treatment protocols and if registered their NCT Number or their corresponding link.

2. Relevant WHO technical department and focal point

This application has been pre-discussed with Bernadette Cappello, Lorenzo Moja, Albert Figueras, Elizabeth de Vries and Andrea Bondi and was additionally reviewed by Bernadette Cappello.

3. Name of the organisation(s) consulted and/or supporting the project

European Society for Paediatric Oncology (SIOPE) and European Clinical Trial Groups

4. International Non-proprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine.

Generic name	**Approval by major regulatory agencies for use in children**	**Dose form included in WHO cEML 2019**
Dactinomycin	INN: Dactinomycin ATC: L01DA01 EMA: *	Powder for injection: 500µg in vial

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Ifosfamide	INN: Ifosfamide ATC: L01AA06 EMA: *	Powder for injection: 500mg vial; 1g vial; 2g vial
Etoposide	INN: Etoposide ATC: L01CB01 EMA: EMEA/H/A-30/1425	Capsule: 50mg; 100mg Injection: 20 mg/ml in 5 ml vial
Carboplatin	INN: Carboplatin ATC: L01XA02 EMA: PSUSA/00000559/201601	Injection: 50mg/5ml; 150mg/15ml; 450mg/45ml; 600 mg/60ml
Cyclophosphamide	INN: Cyclophosphamide ATC: L01AA01 EMA: EMEA-000530-PIP02-11	Powder for injection: 500 mg in vial. Tablet: 25 mg; 50 mg.
Methotrexate	INN: Methotrexate ATC: L01BA01 EMA: EMEA/H/A-31/1463	Powder for injection: 50mg (as sodium salt) in vial. Tablet: 2.5mg (as sodium salt)
Imatinib	INN: Imatinib ATC: L01XE01 EMA: EMEA/H/C/000406	Tablet: 100mg; 400mg
Irinotecan	INN: Irinotecan ATC: L01XX19 EMA: *	Injection: 40mg/2ml in 2 ml vial; 100mg/5ml in 5 ml vial; 500mg/25mL in 25 ml vial
Methylprednisolon	INN: Methylprednisolone ATC: H02AB04 EMA: *	Injection: 40 mg/ml (as sodium succinate) in 1ml single-dose vial and 5ml multi-dose vials; 80 mg/ml (as sodium succinate) in 1ml single-dose vial
Dexamethason	INN: Dexamethasone ATC: H02AB02 EMA: *	Injection: 4mg/ml in 1mL vial (as disodium phosphate salt). Oral liquid: 2mg/5mL Tablet: 2 mg; 4 mg
Hydrocortisone	INN: Hydrocortisone ATC: H02AB09 EMA: *	Powder for injection: 100mg (as sodium succinate) in vial

* For the indicated medicines no EMA number or registration as single compound exists

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5. Dose forms(s) and strength(s) proposed for inclusion; including adult and age-appropriate paediatric dose forms/strengths (if appropriate)

For all above mentioned compounds, the dose forms and concentrations do not differ to the already approved indications.

6. Information supporting the public health relevance

Childhood cancers are markedly different from those which occur in adults [1] (Figure 1). According to the ICD-O-3 classification of tumours in adults, the International Classification of Childhood Cancer, third edition (ICCC-3), classifies tumours into 12 main groups, which are further subdivided into 47 subgroups [2]. Childhood cancer is a rare disease per definition, with approximately 1 to 2 per 10.000 children aged 14 years and younger affected annually in Europe. However, it remains the leading cause of disease-related mortality among children above one year of age. For children under one year, the most common malignancy is neuroblastoma (28.6%), followed by leukaemia (14.4%). For the age group 1 to 14, leukaemia is the most common malignancy (25%), followed by neoplasms of the central nervous system (CNS) (17%) [3].

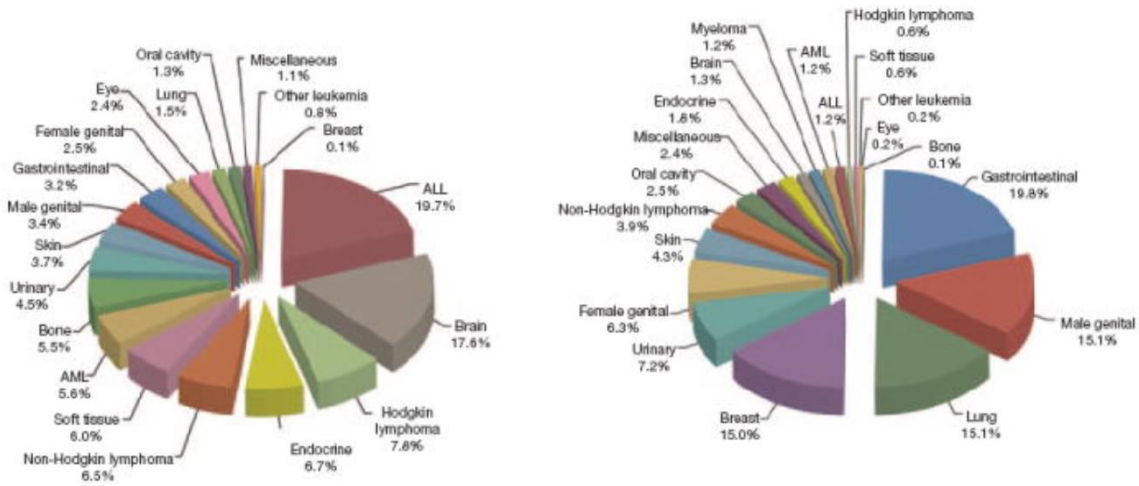

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Figure 1: Frequency of cancer diagnoses and leukaemia subtypes in children and adults. The frequency of cancer types in children (left) and adults (right) on the basis of 2012 Surveillance, Epidemiology and End Results (SEER) data [1] .

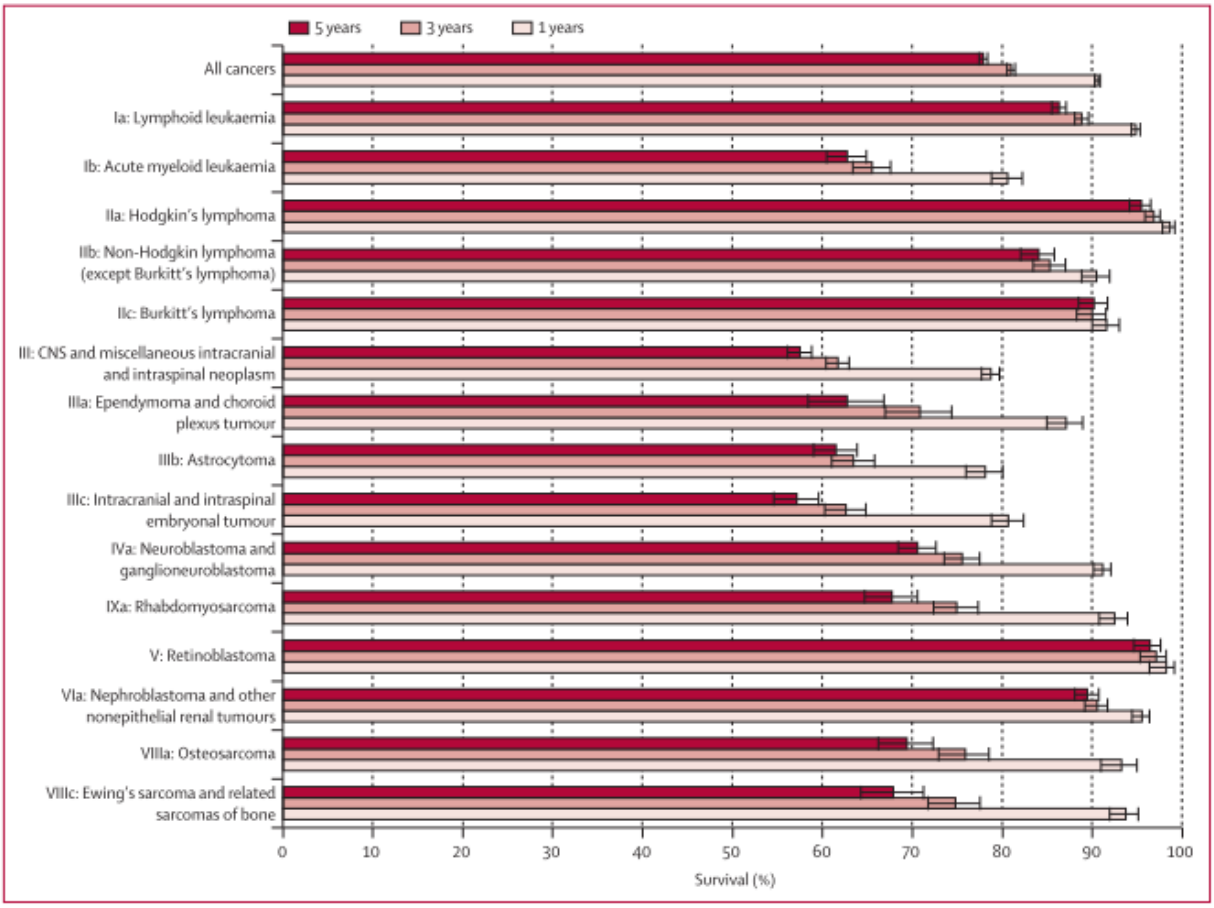

Figure 2: Country-weighted survival by ICCC diagnostic category for European children diagnosed with cancer 2000–07. Includes data for 57 956 cases. Error bars are 95% CI [4]

7. Review of harms and toxicity: summary of evidence of safety

Our proposed medicines are all longstanding with vast experiences in regard to their toxicity profile. Further, usage of these medicines in the treatment of a different malignancy does not change their adverse events and toxicities and should in this sense be considered the same. Nevertheless treatment with chemotherapeutic agents comes along with significant adverse

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events in the acute setting but also in the long-term in cancer survivors and requires a close monitoring [3, 5, 6].

8. Treatment details and reference protocols

Unlike in adult oncology, cancer in children and adolescents is almost exclusively treated according to academic national and international treatment protocols. This is especially true for upfront treatment but often also for relapsed and refractory disease. These treatment protocols are initiated and written by academic experts from the corresponding tumour groups and are further developments of previous protocols. Often these treatment protocols consist of a standard arm that has proven to be effective based on previous experiences, treatment strategies and randomised questions. Many protocols contain one or multiple additional arms with randomised study questions, such as addition of a new compound (e.g. addition of 2-Chloro-2-desoxyadenisone in consolidation of children with high-risk AML) or efficacy of dose reduction (e.g. Daunorubicin in AIEOP-BFM ALL 2009 protocol). Some protocols, in which the randomised question has been answered and no new question emerged, are kept as registries and guidelines and treatment is given according to them. As almost all paediatric patients in Europe are treated according to these international treatment protocols, a high rate of study participation allows research in a group of rare diseases in Europe and assures a high quality of care.

Summary Table of the medicines with new indications and the protocols in which they are used:

Drugs listed in the protocol	**Drugs with new indication**	**Trials including the new drug**	**Trial registration / Publication**
AML (acute myeloid leukemia and acute promyelocytic leukemia)			
All-trans retinoid acid (ATRA) Cytarabine Daunorubicin Idarubicine Methotrexate Mitoxantrone Prednisolone	Etoposide	AML- BFM 2012	EduraCT: 2013-000018-39

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Sorafenib Thioguanin			
Cytarabine Daunorubicin Fludarabine Methotrexate Mitoxantrone	Etoposide	NOPHO-DBH AML 2012	NCT01828489
Cytarabine Idarubicin Mitoxantrone	Etoposide	ML DS 2006	EduraCT: 2018-002988-25
Nephroblatoma			
Dactinomycin Doxorubicin Vincristine	Carboplatin Cyclophosphamide Etoposide	SIOP 2001 / GPOH Protocol, Version 4.0	NCT00047138
Dactinomycin Doxorubicin Melphalan Vincristine	Carboplatin Cyclophosphamide Etoposide Ifosfamide Irinotecan	Umbrella SIOP-RTSG 2016	EduraCT: 2016-004180-39 DRKS-ID: DRKS00011208
Acute Lymphoblastic Leukemia			
Cyclophosphamide Cytarabine Daunorubicin Dexamethasone Doxorubicin Etoposide Fludarabine Idarubicin Mercaptopurine Methotrexate Nelarabine Predinsone Pegaspargase Vincristine	Imatinib	ALLTogether	NCT03911128
Cyclophosphamide Cytarabine Daunorubicin Doxorubicin Dexamethasone Etoposide Hydrocortisone Ifosfamide Mercaptopurine Methotrexate Pegaspargase Tioguanine Vincristine	Imatinib	EsPhALL 2017	NCT00287105
Ewing			
Cyclophosphamide Doxorubicin Etoposide Ifosfamide Vincristine	Dactinomycin	EICESS-92	Paulussen M, Craft AW, Hackshaw, et al. J Clin Oncol 2008;26(27):4385-93.
Busulfan Cyclophosphamide Doxorubicin Etoposide Ifosfamide	Dactinomycin	Euro Ewing 2012 protocol	NCT00020566 Brennan B, Kirton L, Marec-Berard P, et al. J Clin Oncol 2020;38(15):11500.

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Melphalan Vincristine			
Busulfan Cyclophosphamide Doxorubicin Etoposide Ifosfamide Melphalan Vincristine	Dactinomycin	Euro Ewing 99	Le Deley MC, Paulussen M, Lewis I, et al. J Clin Oncol 2014;32:2440-8 Whelan J, Le Deley MC, Dirksen U, Le Teuff G, Brennan B, Gaspar N, et al. J Clin Oncol 018;36(31):JCO2018782516
Ovarian and Testicular Germ Cell Tumors			
Cisplatin Etoposide Ifosfamide Thiotepa	Carboplatin	MAKEI 05	
Cisplatin Etoposide Ifosfamide	Carboplatin	MAKEI V	EudraCT 2016-001784-36
Cisplatin Etoposide Bleomycin	Carboplatin	Interim Guidelines from CCLG	https://www.cclg.org.uk/write/MediaUploads/Member%20area/Treatment%20guidelines/614_Extracranial_GCT_Guidance_updated_June_2018.pdf
Burkitt lymphoma			
Cyclophosphamide Cytarabine Doxorubicin Prednisolone Prednisone Vincristine	Dexamethasone Ifosfamide Methotrexate	LBL 2018	NCT04043494
Cyclophosphamide Cytaraine Doxorubicin Etoposide Prednisolone Prednisone Vincristine	Hydrocortisone Methylprednisolone Methotrexate	Inter-B-NHL Ritux 2010	Minard-Colin V. et al. N Engl J Med. 2020 Jun 4; 382(23): 2207–2219. https://www.skion.nl/workspace/uploads/c1_inter-b-nhl_ritux_2010_v1-1_9_sep__2011.pdf
Osteosarcoma			
Cisplatin Doxorubicin Ifosfamide Methotrexate	Etoposide	The French OS 2006 protocol	NCT00470223 Gaspar N, Occean B, Pacquement, et al. Eur J Cancer 2018;88:57-66.
Rhabdomyosarcoma			
Cyclophosphamide Dactinomycin Doxorubicine Ifosfamide Temozolomide Vincristine Vinorelbine	Irinotecan	EpSSG FaR-RMS Study	EudraCT: 2018-000515-24
Temozolomide Vincristin	Irinotecan	VIT-0910	NCT01355445, Defachelles, A.S., et al. Journal of Clinical Oncology, 2019. 37(15_suppl): p. 10000-10000.

Abbreviations: DRKS, German Clinical Trials Register; EudraCT, European Union Drug Regulating Authorities Clinical Trials Database; NCT, ClinicalTrials.gov (US National Library of Medicine) identifier

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9. Conclusion

Based on the data summarised in this document, we propose to extend the indications listed on the WHO cEML 2021 for a selection of medicines highly relevant for the treatment of children with cancer in Europe. We truly believe that an inclusion will lead to a more accurate picture of the treatment strategies for childhood cancers and would pave the way towards establishing better availability and access to medicines for all children and adolescents with cancer in Europe. As these proposed medicines already exist within the WHO cEML2019, we foresee our data rather as complementing and enriching, and we look forward to receiving your valuable feedback and further deepening of our collaborative scope on future WHO cEML for childhood cancers.

10. References

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