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SIOPE and ESOP recommendations for extemporaneous compounding of oral liquid medicine formulations in paediatric oncology

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ABSTRACT

Introduction: Scarcity of age appropriate formulations for orally administered medicines for paediatric malignancies is a critical and ongoing issue which necessitates urgent solutions. According to JARC Survey 27 % of oral medicines were never available in child-friendly formulations (Vassal et al., 2021 [2]). Pharmacists from the European Society of Oncology Pharmacy Global (ESOP) and the European Society for Pediatric Oncology (SIOPE) have collaborated to provide a document summarising literature data on this topic and a set of practical instructions on the preparation of extemporaneous oral liquid medicines.

Material and methods: Literature review was conducted for the preparation of oral medicines for paediatric cancer, through Pubmed 2.0. A table was drawn up with necessary information for medicine preparation. We adapted the classification model of the molecule stability ranking of the International database of stability for injectable drugs, Stabilis® (Class A–C).

Results: A total of 126 articles were selected and analysed. All commercially available marketed liquid oral medications used in paediatric cancer were overviewed using globally accessible drug databases and compiled in a table with appropriate indications. Based on the literature review, 28 formulations for 13 different active ingredients for chemotherapy and 35 formulations for 16 different active ingredients for supportive therapy were compiled.

Conclusions: Development of child-appropriate formulations of anticancer medicines by the pharmaceutical industry should be incentivised towards marketing authorisation to enhance accessibility. The results of this study could help facilitate creation of European standards for extemporaneous preparation and persuade researchers in the field of paediatric oncology on the way forward.

1. Introduction

The majority of medicines used for the treatment of paediatric malignancies were originally developed for adult cancer patients. This implies that medicines are often prescribed off-label without age-appropriate formulations for children [1]. In recent decades, the quality, safety, and efficacy of these medicines have been established through prospective international cross-border academic clinical

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studies, thus today the majority is commonly used in European treatment protocols [2]. Nevertheless, tailoring the most appropriate formulation, dose and route of administration to the treatment in order to increase compliance and safety for all paediatric patients with cancer is an existing challenge [7,8].

Achieving equal access to essential and novel anticancer medicines for all children and adolescents across Europe at all times has been one of the key objectives of the European childhood cancer community [3]. In 2018, under the EU Joint Action on Rare Cancers (JARC) (724161) [9], a pan-European survey was sent to physicians, pharmacists, and parent representatives from 34 different countries. The survey found that the lack of appropriate child-friendly formulations was one of the main issues in the availability of oral anticancer medicines in paediatric oncology [2].

The absence of appropriately manufactured child-friendly oral formulations, especially in paediatric oncology is a global emergency which requires urgent solutions [10]. Extemporaneous compounding in hospitals and community pharmacies has enabled the ad-hoc preparation of age-appropriate dosage forms when suitable authorised medicines are not available [4,5]. Since many medicines are not licensed for use in paediatric populations, the marketing authorisation holder does not ordinarily produce age-appropriate dosage forms for the market [6]. Hence, community and hospital pharmacy departments have been bound to find solutions and narrow the gaps through research to establish the most appropriate scientific methods to safely prepare ad hoc liquid formulations.

Despite this need, without harmonised European standards to facilitate research opportunities to develop new formulations, their capacity is overstretched. Thus, one of the objectives of the JARC was to assess the accessibility of essential therapies for children and adolescents with cancer in Europe and to provide recommendations to the European and national governments based on the generated evidence.

Hence, under the European Society for Paediatric Oncology (SIOPE) Access to Medicines Project, both SIOPE and the European Society of Oncology Pharmacy (ESOP) produced the first-ever European guidelines to help harmonise and promote the preparation of suitable oral childhood cancer medicines to maximise achieving the best possible therapeutic benefit for patients. Written instructions are restricted to extemporaneous oral liquid formulations, and they are aimed at providing meticulous guidance to healthcare professionals on their in-detail preparation. In addition, the recommendations also outline an up-to-date overview of post-marketed child-friendly formulations of the essential medicines developed by the industry in recent years. According to Quality Standards for Oncology Pharmacy (QuapoS), the preparation of oral chemotherapy agents requires not only separate GMP facilities with a certain degree of ventilation, biosafety cabinet and negative pressure, but also highly trained staff, good documentation practice, clear procedures and quality control [7].

2. Material and methods

2.1. Study design and working steps

SIOPE and ESOP joined forces to review published literature and strategies concerning the preparation of extemporaneous oral liquid medicines for children with cancer. The study was conducted by members of the ESOP and SIOPE Working Group of pharmacists in paediatric oncology, SIOPE Board Members, ESOP Board Members, and additional pharmacists who were later assigned to review the group's final list of instructions and written recommendations.

2.2. Literature search and analysis

Literature data was gathered from PubMed (period 1987–2022), manufacturer data bases of formulas (references Fagron etc), Stabilis database, paediatric hospital pharmacies open resources, Google Scholar and conference papers. In total, 126 publications were reviewed and analysed to compile the most relevant, recent and accessible evidence currently available. Some evidence on marketing hurdles of authorised anticancer medicines for paediatric indication and their off-label use were also observed. Challenges with the preparation of oral anticancer and supportive care medicine formulations for children were identified (Table 1).

2.3. Instructions for medicine compounding

In the second part of the study, a sample table was created with the aim to provide an overview of the necessary information considered a prerequisite for the preparation of oral liquid medicines in paediatric oncology. Please refer to Table 2.

The retrieved compounding instructions were evaluated, compared to each other (where applicable) and standardised according to the sample table. Where more than one similar instruction for an API was found, a formula with diverse base suggestions was chosen as the preferred. Furthermore, all the API information was added to the preambles of every medicine compounding instruction. Prevalent and most commonly used brands of syrup and suspension bases were listed and described separately from the tables. The formulations were ranked based on the level of collected stability evidence (excluding safety and efficacy of the medicinal product) into 3 distinct classes, please see Table 3.

3. Results

The Essential medicines list by SIOPE contains 26 anticancer and 21 supportive medicines prescribed orally. All available industry manufactured liquid oral medicines used in paediatric cancer were collated, analysed and compiled according to the sample table. Only 25 medicines were marketed in a child appropriate formulation: 10 anticancer and 15 supportive care medicines (see Tables 4 and 9). The current version of the extemporaneous compounding guidelines encompasses detailed instructions with outsourced evidence on how to prepare 29 oral medicines (chemotherapeutic agents and supportive care medicines) in 63 different child-friendly formulations (solutions, suspensions and syrups) for childhood cancer patients. When compounding a medicine, the best practice is to use the APIs. Compounding from marketed tablets or capsules could decrease the stability of liquid medicines because of excipients, and thus cause harm to patients due to adverse effects. For example, harmful excipients such as sodium benzoate are highly toxic for newborns, and may increase the risk of jaundice, hypersensitivity and kernicterus in newborn babies [29–31]. However, due to the lack of access to the most API ingredients there are still many formulas which include solid industry manufactured medicines as raw materials. Out of all the examined medicines, 36 formulas include the use of API in a powder form, 19 formulas involve preparation from a marketed capsule or tablet and 8 formulas require the use of marketed intravenous medicines (See Tables 5 and 6). See Table 7 for the distribution of formulas by classes of evidence. Preparation instructions for ad-hoc extemporaneous compounding were found for most medicines, see Table 8.

4. Discussion

The paediatric medicine market is comparatively small and segmented by age groups [11]. Conducting clinical trials for the development of new drug formulations for children is costly, time-consuming and ethically complex. However, the last 50 years have demonstrated that academic clinical trials are feasible and contributed to significantly improving standard treatments and survival. There is a low or no return on investment for the pharmaceutical industry when developing paediatric medicines. This is the reason why regulatory initiatives in the US and Europe have been set up over the last 30 years to ensure availability of the best medicines for children [12]. The obligations, incentives and

Table 1
SIOPE and ESOP recommendations to boost access to child-friendly medicines in Europe.

Incentivise pharmaceutical industry to develop and market child-friendly oral formulations of essential anticancer medicines
Ensure sustained public funding for academia to systematically run clinical trials on child-friendly oral formulations of medicines
Conduct research on stability studies of extemporaneously compounded medicines in paediatric oncology that will further underpin the quality and efficacy of medicines
Allocate research opportunities in 3D medicine printing, a robust and adaptive technology, to accelerate access to personalised therapy for children
Explore compounding opportunities of novel anticancer medicines for children entering the market in the coming years
Evaluate the current role of pharmacists in paediatric oncology and create a dedicated career pathway that will be tailored to the patients' needs and updated over the time

Table 2
Required information for medicine compounding.

DOSAGE	Clarify concentration and measured frequency of a dose of a medicine
ADMINISTRATION	Specify the path by which the medicine is taken into the body
FORMULATION	Name the form of the medicine
QUANTITY	Indicate the final quantity of the medicine
INGREDIENTS	List available ingredients for the medicine (including amount)
COMPOUNDING INSTRUCTIONS	Provide guidance to pharmacists in relation to the compounding of medicines
LABELLING, PACKAGING AND STORAGE	Ensure all packaging and labelling of the compounded product is appropriate and complete, specify the storage conditions
BEYOND-USE DATA (BUD)	Describe the date or time after which a compounded preparation shall not be stored or transported
QUALITY CONTROL	Ensure that compounded medicine complies with the relevant quality standards

Table 3
Classification of extemporaneous formulations.

Class*	Description
Class A	Stability and formulation study is published in a peer-reviewed journal, with stability margin less than 5 %
Class B	Collated formulation and dosage information has incomplete data (lacks data on degradation or data on the sensitivity of the method) in a peer-reviewed journal or a paper, with stability margin equal to or less than 10 %
Class C	Stability data originates from a non-peer reviewed source and is currently based on experts' opinion or first hand experience.

* Classification model of Stabilis® data base molecule stability ranking was adapted.

rewards have not properly addressed the needs for new anticancer medicines, including child friendly formulations [2]. The specific Paediatric Use Marketing Authorisation (PUMA) of the EU Paediatric Medicine Regulation [12] failed to deliver on the needed age appropriate formulations of off-patent medicines for children. In recent years, there has been an inclination in the pharmaceutical industry to minimise the diversity and number of dosage forms being marketed [13]. Hence, therapeutic advances (e.g. modified-release forms) are seldom available for the paediatric population and there is a need to incentivise manufacturers in continuing child friendly medicine research.

Primarily, the pharmacist must investigate the availability of licenced products with appropriate formulations and obtain them for children, since they are clinically evaluated for their safety and efficacy. When no relevant formulation is commercialised, compounding must be performed by the national rules [14]. There are inequalities in access to newly approved medicines. Compounding is needed in some countries even if an age-appropriate formulation is centrally authorised in Europe. Legislation regulating the compounding of extemporaneous preparations is not harmonised among European countries, although some European countries (e.g. the Netherlands, Germany, Ireland, Switzerland) and pharmacy societies have already prepared their guidelines. This inconvenience is partially resolved by Resolution CM/Res(2016)1 of the Council of Europe on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients [15].

However, as access to the necessary ingredients for compounding is not the same across Europe, not all European regions have the resources to compound such medicines with a resultant urgency to enhance their access to this population. A good example of a promising initiative to tackle the issue of paediatric formulations is the WHO Global Accelerator for Paediatric Formulations Network (GAP-F) which has been created to respond to paediatric treatment gaps, with major achievements for the treatment of children with HIV [32]. This programme aims to develop medium- and long-term priorities for medicine development, accelerating access to optimal formulations in the context of fragmented markets [16,17].

Compounding an oral liquid medicine requires determining whether a solution, syrup or suspension is the best option for any particular medicine. Making a decision is based on the pharmaco-chemical and pharmacological properties of the drug, the duration of therapy, as well as solubility, stability of the active ingredient in its vehicle and palatability.

In addition, concealing the taste and smell of the medicine is a hurdle that may be quite costly [17]. During the preparation of hazardous drugs, special precautions for healthcare staff must be adopted as the particles of highly toxic substances may be released into the environment [18]. According to Quality Standards for Oncology Pharmacy (QuapoS), the preparation of oral chemotherapy agents requires not only separate GMP facilities with a certain degree of ventilation, biosafety cabinet and negative pressure, but also highly trained staff, good documentation practice, clear procedures and quality control [7].

For the purposes of this study, we mainly focused on the essential anticancer and supportive care medicines for children with cancer, according to the SIOPE Access to Medicines Project, except for newer classes of drugs (Tyrosine Kinase Inhibitors (TKI), Mitogen-Activated protein Kinase kinase (MEK) inhibitors etc). Literature already shows that specialists are solving the problems of dosing TKIs and other similar molecules, many of which have poor solubility [2]. For example, there are preparation instructions and stability data for imatinib oral solution [19] and recommendations providing a decision tree on how to manipulate solid oral dosage forms of TKIs [20].

The formulated extemporaneous compounding instructions were categorised into 3 classes. According to the collated and classified evidence, there is a crucial need for dedicated academic-driven research opportunities on the stability studies of the extemporaneous formulations in paediatric oncology, since from 63 gathered instructions only 10 were classified with A level evidence, while 7 have B level evidence. The remaining 46 have only C level evidence. Ranking of the formulations in the 3 classes shows no linear correlation to the safety and efficacy of the extemporaneous medicines, but indicates the necessity for conducting more research on the stability data that would complement the quality of the written compounding instructions. Further to it, the impurity levels of examined medicines were not assessed, hence precautionary measures must be taken into account for unforeseen pharmacological effects. In addition, the reviewed publications under this project imposed impediments to determining their compliance with ICHQ3B and ICHM7 recommendations. Thus, a risk study must be carried out for each case before compounding and a commercial form should always be prioritised. Furthermore, the study revealed limitations on the choice of the route of administration, concentration of excipients and volume of

Table 4
List of oral liquid marketed anticancer and supportive medicines.

INN (ATC code)	Brand name, year of authorisation	Indications	Dose	Form
Amphotericin (A07AA07)	Ampho-moronal, 2005	Local treatment and prophylaxis of gastrointestinal fungal infections	100 mg/ml – 50 ml	Oral suspension
Aciclovir (J05AB01)	Zovirax, 1984	Treatment of herpes simplex virus infections, varicella, prevention of recurrent herpes in immunocompetent patients	200 mg/5 ml – 125 ml	Oral suspension
Ciprofloxacin (J01MA02)	Ciproxin, 1996	Treatment of infections	250 mg/5 ml – 30 ml	Granules and solcent for oral suspension
Clonazepam (N03AE01)	Rivotril, 1976	Epilepsy, typical and atypical absences	2,5 mg/ml – 10 ml	Oral solution (drops)
Sulfamethoxazole/ Trimethoprim (J01EE01)	Biseptol, 1996	Pneumocystis jiroveci prophylaxis, other infections	200 mg/40 mg/ 5 ml - 80 ml	Powder for a suspension
Cyclosporine (L04AD01)	Sandimmun Neoral, 2013	Solid organ transplantation, Bone marrow transplantation, Endogenous uveitis, Nephrotic syndrome, Rheumatoid arthritis, Psoriasis, Atopic dermatitis	100 mg/ml - 50 ml	Oral solution
Dexamethasone (H02AB02)	Dexamethasone Martindale pharma, 2011	Endocrine disorders, allergy, Acute lymphoblastic Leukaemia Histiocytosis/HLH Non-Hodgkin Lymphoma	0,4 mg/ml – 150 ml	Oral solution
Everolimus (L01EG02)	Votubia, 2011	Low Grade Glioma; EBMT; Renal angiomyolipoma associated with tuberous sclerosis complex (TSC), Subependymal giant cell astrocytoma (SEGA) associated with TSC	1 mg, 2 mg, 3 mg, 5 mg	Dispersible tablets for a suspension in water
Fluconazole (J02AC01)	Diflucan, 2001	Fungal infections treatment and prophylaxis, children: mucosal candidiasis, invasive candidiasis, cryptococcal meningitis, candidiasis prophylaxis.	5 mg/ml - 180 ml; 10 mg/ml and 40 mg/ml	Oral solution, powder for oral suspension
Hydroxycarbamide (L01XX05)	Xromi, 2019	Prevention of vaso-occlusive complications of Sickle Cell Disease in patients over 2 years of age; Chronic myelogenous leukaemia	100 mg/ml - 150 ml	Oral solution
Hydrocortisone (H02AB09)	Cortef Oral suspension (USP 2003)	Acute Myeloid Leukaemia Non-Hodgkin Lymphoma	10 mg/5 ml - 118 ml	Oral suspension
	Alkindi, 2018	Replacement therapy of adrenal insufficiency in infants, children and adolescents	0,5 mg, 1 mg, 2 mg, 5 mg	Granules in capsules for opening
Itraconazole (J02AC02)	Sporanox, 1996	Prophylaxis and treatment of candidosis, deep fungal infections	10 mg/ml – 150 ml	Oral solution
Larotrectinib (L01EX12)	Vitrakvi, 2019	Treatment of adult and paediatric patients with solid tumours that display NTRK gene fusion	20 mg/ml – 100 ml	Oral solution
Lorazepam (N05BA06)	Ativan, Lorazepam Thame 2016	Anxiety management, seizures, premedication	1 mg/ml – 150 ml	Oral solution
Mercaptopurine (L01BB02)	Xaluprine (Nova Laboratories, EMA 2012) Purixan (Nova laboratories, USA)	Acute Lymphoblastic Leukaemia, Acute Myeloid Leukaemia, Histiocytosis/HLH, Non-Hodgkin Lymphoma	20 mg/ml - 100 ml	Oral suspension
Methotrexate (L04AX03)	Methotrexate Rosemont, 2015	Polyarthritic forms of active, severe juvenile idiopathic arthritis in adolescents and children aged 3 years and over; Severe, treatment-refractory, disabling psoriasis; Acute lymphoblastic leukaemia, Acute Myeloid Leukaemia CNS Tumours (non-LGG), Bone marrow transplantation, Histiocytosis/HLH, Non-Hodgkin Lymphoma, Osteosarcoma, Soft Tissue Sarcoma	2 mg/ml - 35 ml 2 mg/ml - 65 ml	Oral solution
	Jylamvo, 2017		2 mg/ml - 60 ml	Oral solution
Metoclopramide (A03FA01)	Metoclopramide hydrochloride Rosemont, 1998	Gastroesophageal reflux, Chemotherapy induced nausea and vomiting	5 mg/ml – 150 ml	Oral solution
Metronidazole (J01XD01)	Metronidazole Rosemont, 1984	Prophylaxis and treatment of anaerobic bacteria infections	200 mg/5 ml - 100 ml	Oral suspension
Mycophenolate mofetil (L04AA06)	Cellcept, 2021	In combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal, cardiac or hepatic transplants	1000 mg/5 ml - 175 ml	Powder for oral suspension
Ondansetron (A04AA01)	Ondansetron Advanz pharma, 2011	Chemotherapy induced nausea and vomiting for children >6 months	4 mg/5 ml - 50 ml	Syrup
Prednisolone (H02AB06)	Prednisolone Advanz pharma, 2013	Immunosuppression in transplantation etc	10 mg/ml – 30 ml	Oral solution
Sirolimus (L04AA10)	Rapamune, 2001	Organ rejection prophylaxis for adults with renal transplant; sporadic lymphangio-leiomyomatosis.	1 mg/ml - 60 ml	Oral solution
Tacrolimus (L04AD02)	Modigraf, 2021	Bone marrow transplantation	0,2 mg and 1 mg sachets	Granules for oral suspension
Temozolomide (L01AX04)	Kizfizo (Early Access to Medicines Scheme in Europe)	CNS Tumours (non-LGG), Neuroblastoma, Soft Tissue Sarcoma,Renal Tumours. Trials on glioma, relapsed or refractory neuroblastoma, rhabdomyosarcoma, medulloblastoma, Ewing sarcoma.	40 mg/ml	Oral suspension
Ursodeoxycholic acid (A05AA02)	Ursofalk, 2004	Treatment of primary biliary cholangitis, dissolution of radiolucent gallstones; hepatobiliary disorders	250 mg/5 ml – 250 ml	Oral suspension

intake following the EMA guidelines [21,22]. Although the focus of the study is on extemporaneous compounding of medicines for childhood cancer patients, we observe additional methods for adjusting the formulations which were not addressed in this study. Sometimes there is no other possibility than to mix a medicine with liquid or food, however in that case information about the bioavailability and stability is required [23]. Hence, more sophisticated formulation strategies such as encapsulation of drug particles are highly promising.

Since the law and practice of medicines compounding differ between and within countries, the role of pharmaceutical specialists tends to be different as well. However, it is understood that for further quality improvement and harmonisation of compounding processes between countries, it is necessary to carry out more studies of stability, safety and pharmacokinetics of extemporaneous preparations. Thus, it would be critical for these purposes to ensure rightful allocation of resources to academia to conduct the research. As a result, these guidelines should be

Table 5
List of adapted oral liquid formulations for essential anticancer medicines as available in publications.

Essential anticancer medicines				
Medicine name	**Indication**	**Original formulation**	**Adapted oral formulation for compounding**	**Stability Class (A–C)**
Busulfan	Ewing sarcoma, high risk neuroblastoma, Langerhans cell histiocytosis, HLH, refractory cytopenia of childhood, MDS, allogeneic HSCT	Tablet	Suspension	C
Cyclosporine	MDS, allogeneic HSCT, prevention of GvHD, MDS, severe aplastic anaemia	API	Suspension	C
		Capsule	Suspension	C
Cyclophosphamide	Acute lymphoblastic leukaemia, CNS tumours (non-LGG), low-grade glioma, EBMT, Ewing sarcoma, histiocytosis/HLH, neuroblastoma, non-hodgkin lymphoma, rare tumours renal tumour, hodgkin lymphoma, soft tissue sarcoma	Powder for injection	Suspension	C
		Powder for injection	Suspension	B
Etoposide	Acute lymphoblastic leukaemia, acute myeloid leukaemia, CNS tumours (non-LGG), EBMT, Ewing sarcoma, rare tumours, Germ cell tumours, histiocytosis/HLH, non-hodgkin lymphoma, renal tumours, neuroblastoma, hodgkin lymphoma, osteosarcoma retinoblastoma, soft tissue sarcoma, liver tumours	Solution for injection (2 formulations)	Solution	B
Hydroxycarbamide	Chronic myelogenous leukaemia	Capsule	Suspension	A
Lomustine	CNS tumours (non-LGG)	API (4 formulations)	Suspension	C
Mercaptopurine	Acute lymphoblastic leukaemia, acute myeloid leukaemia, histiocytosis/HLH, non-hodgkin lymphoma	Tablet	Suspension	C
		API	Suspension	C
Methotrexate	Acute lymphoblastic leukaemia, acute myeloid leukaemia, CNS tumours (non-LGG), EBMT, histiocytosis/HLH, non-hodgkin lymphoma, osteosarcoma, soft tissue sarcoma	API (2 formulations)	Suspension	C
		Solution for injection	Solution	A
Mycophenolate mofetil	Bone marrow transplantation	Capsule	Suspension	A
Procarbazine	Hodgkin lymphoma	API (2 formulations)	Suspension	C
Tacrolimus	EBMT	Capsule	Suspension	A
		API (4 formulations)	Suspension	C
Temozolomide	CNS tumours (non-LGG), neuroblastoma, soft tissue sarcoma	Capsule	Suspension	B
Tioguanine	Acute lymphoblastic leukaemia, acute myeloid leukaemia, non-hodgkin lymphoma	Tablet (2 formulations)	Suspension	C

Table 6
List of adapted oral liquid formulations for essential supportive care medicines as available in publications.

Essential supportive care medicines				
Medicine name	**Indication**	**Original formulation**	**Adapted oral formulation for compounding**	**Stability Class (A–C)**
Allopurinol	Tumour lysis syndrome prophylaxis	Tablet (2 formulations)	Suspension	C
		API	Suspension	B
Amphotericin	Antimycotic	API	Suspension	A
Ciprofloxacin hydrochloride	Antibiotic	API (2 formulations)	Suspension	C
Clonazepam	Anxiolytic	API (2 formulations)	Suspension	C
Dexamethasone	Acute lymphoblastic leukaemia, histiocytosis/HLH, non-hodgkin lymphoma	Tablet (2 formulations)	Suspension	C
		solution for injection	Suspension	B
Fluconazole	Antimycotic	API	Suspension	A
Hydrocortisone	Acute myeloid leukaemia, non-hodgkin lymphoma	Tablet (3 formulations)	Suspension	C
Itraconazole	Antimycotic	API (2 formulations)	Suspension	C
Calcium folinate	High-dose methotrexate supportive therapy	Solution for injection	Solution	A
Lorazepam	Anxiolytic	API (2 formulations)	Suspension	C
Mesna	Cyclophosphamide, ifosfamide supportive therapy	Solution for injection	Syrup	A
Metronidazole benzoate	Antibiotic, antiprotozoal	API (2 formulations)	Suspension	C
Ondansetron	Chemotherapy induced nausea and vomiting	Tablet (2 formulations)	Suspension	C
Prednisone	Acute lymphoblastic leukaemia, hodgkin lymphoma	Tablet/API	Suspension	A
Prednisolone	Acute lmphoblastic leukaemia, acute myeloid leukaemia, histiocytosis/HLH, non-hodgkin lymphoma, EBMT	API (3 formulations)	Suspension	C
Sulfamethoxazole + trimetoprim	Antibiotic	API	Suspension	B
Ursodeoxycholic acid	Hepatobiliary disorders	API (4 formulations)	Suspension	C

Table 7
Total number of adapted preparation instructions for chemotherapeutic and supportive medicines*.

Level of evidence \class	Chemotherapy	Supportive medicines
Class A	4 formulations (hydroxycarbamide, methotrexate, mycophenolate mofetil, tacrolimus)	6 formulations (amphotericin, fluconazole, calcium folinate, mesna, 2 prednisone)
Class B	4 formulations (cyclophosphamide, 2 etoposide, temozolomide)	3 formulations (allopurinol, dexamethasone, Sulfamethoxazole/ Trimethoprim)
Class C	20 formulations (busulfan, 2 cyclosporine, cyclophosphamide, 4 lomustine, 2 mercaptopurine, 2 methotrexate, 2 procarbazine, 4 tacrolimus, 2 tioguanine)	26 formulations (2 allopurinol, 2 ciprofloxacin, 2 clonazepam, 2 dexamethasone, 3 hydrocortisone, 2 itraconazole, 2 lorazepam, 2 metronidazole, 2 ondansetron, 3 prednisolone, 4 ursodeoxycholic acid)

* This table does not include the marketed formulations of childhood cancer medicines.

Table 8
SIOPE essential medicines for childhood cancer for oral administration.

Orally used medicines	SIOPE essential anticancer medicines list	SIOPE essential supportive care medicines list
Do have extemporaneous age appropriate formulation and instructions	Mercaptopurine, methotrexate, tioguanine, mycophenolate mofetil, tacrolimus, procarbazine, hydroxycarbamide, temozolomide, lomustine, cyclophosphamide, etoposide, busulfan, cyclosporine	Dexamethasone, prednisolone, amphotericine, Sulfamethoxazole/ Trimethoprim, fluconazole, itraconazole, metronidazole, ciprofloxacin, aciclovir, ursodeoxycholic acid, allopurinol, clonazepam, lorazepam, ondansetron, mesna, calcium folinate
Do not have extemporaneous age appropriate formulation and instructions	Imatinib, dasatinib, nilotinib, ponatinib, crizotinib, larotrectinib, vinorelbine, 13-cis retinoic acid, sirolimus, arsenic trioxide, everolimus, mitotane, idarubicin	Prednisone, methylprednisolone, aciclovir, tropisetron, metoclopramide

regularly reviewed and updated based on data from such studies.

With novel anticancer medicines gradually entering the market in recent years, there is a growing need to explore their child-friendly counterparts. Furthermore, 3D medicine printing is rapidly developing and promises to demonstrate a significant benefit to the historical extemporaneous compounding. Such a robust and adaptive technique could accelerate access to personalised therapy for all paediatric cancer patients [24,25]. Scientific publications and recent industry strategies indicate a clear shift from liquid dosage forms to novel solid dosage forms [26]. This new technology improves palatability and provides flexibility in geometry of the child friendly dosage form and it could also permit cost-effective individualised treatment options. Healthcare professionals and researchers believe 3D printed forms would be useful in paediatrics due to high molecular variability of tumours and precision medicine development. However, the high necessity for more research opportunities in this field is evident [27–29].

5. Conclusions

There is a need to incentivise the development and marketing authorisation of child-friendly oral formulations of anticancer medicines by the pharmaceutical industry. Compounding should be a temporary alternative to address urgent needs of children. The results from this SIOPE and ESOP study could help bridge the gaps in the preparation of extemporaneous formulations in paediatric oncology, facilitate standardised European guidelines on paediatric cancer medicine compounding, and support and guide stakeholders in the field of paediatric oncology on the way forward. There is a pressing urgency to delve into further exploration of the stability data for the provided medicines, 3D medicine printing, and compounding opportunities of novel medicines coming to the market. The expertise of pharmacy specialists in paediatric oncology multidisciplinary teams should be harnessed to tailor medicine preparation to specific needs of patients. Finally, these recommendations should be updated regularly with new and changing evidence based practice or research data.Access our workgroup recommendations in the table below (Table 1):

Table 9
List of collected preparation instructions of essential medicines with and without marketed age-appropriate oral formulations.

	Not marketed	Marketed
Anticancer medicines	Tioguanine, procarbazine, lomustine, cyclophosphamide, etoposide, busulfan, imatinib, dasatinib, nilotinib, ponatinib, crizotinib, vinorelbine, 13-cis retinoic acid, arsenic trioxide, mitotane, idarubicin	Cyclosporine, everolimus, hydroxycarbamide, mercaptopurine, methotrexate, mycophenolate mofetil, tacrolimus, sirolimus, larotrectinib, temozolomide (early access programme)
Supportive medicines	Allopurinol, prednisone, methylprednisolone, tropisetron, mesna, calcium folinate	Sulfamethoxazole/ Trimethoprim, dexamethasone, fluconazole, hydrocortisone, metronidazole, ondansetron, prednisolone, amphotericine, itraconazole, ciprofloxacin, ursodeoxycholic acid, clonazepam, lorazepam, ondansetron, aciclovir

Please see all the formulations and the broader presentation of the topic in the main document attached in supplements.

Contributors

GV and SK contributed to the conceptualisation of the project; and writing, review, and editing of the manuscript. SB and MO contributed to the coordination, guidance, and supervision of the study conduction and data collection; and writing, review, and editing of the manuscript. MA contributed to the writing, review, and editing of the manuscript. TB, LH and CN contributed to reviewing the manuscript. SB and MO accessed and verified the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Data sharing

The in-detail description of each instruction for the preparation of oral liquid medicines for children with cancer, including the evidence collected, are available in full in the annexe.

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CRediT authorship contribution statement

Maxime Annereau: Writing – review & editing. **Tiene Bauters:** Writing – review & editing. **Laszlo Horvath:** Writing – review & editing. **Chahinez Nehal:** Writing – review & editing. **Sherif Kamal:** Supervision. **Gilles Vassal:** Supervision. **Svetlana Buraja:** Writing – review & editing, Writing – original draft, Methodology. **Marko Otsokolhich:** Writing – review & editing, Writing – original draft, Methodology.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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