European Medicines Agency
Evaluation of Medicines for Human Use

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OVERVIEW OF COMMENTS RECEIVED ON LIST OF PAEDIATRIC NEEDS ONCOLOGY I (CYTOTOXIC THERAPY)

Table 1: Organisations that commented on the draft Guideline as released for consultation

	Name of Organisation or individual	Country
1	Universitaetsklinikum Carl Gustav Carus, Prof. Dr. med. Meinolf Suttorp	Germany
2	Institut Gustave Roussy, Villejuif, Gilles Vassal	France
3	ICCCPO Secretariat (The International Confederation of Childhood Cancer Parent Organisations)	Netherlands
4	Consorzio per Valutazioni Biologiche e Farmacologiche	Italy
5	ITCC Innovative Therapies for Children with Cancer	European Consortium
6	TEDDY – Task force of Europe for Drug Development of the Young	Italy
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Table 2:Discussion of comments

GENERAL COMMENTS - OVERVIEW	
Three drugs commonly given to children are still missing in this list: 1. Busulfan orally or intravenously is part of several conditioning regimens in children undergoing haematopoietic stem cell transplantation and may in rare cases be used as second or third line treatment of chronic myeloid leukemia (CML). 2. Hydroxyurea orally is used as first or second line treatment in children with CML as well as in some patients with sickle cell anemia. 3. Imatinib mesylate is used as first line treatment for children with CML.	As Imatinib is already authorised in children > 3 years in the UK, the PEG considers that there is currently no additional need.
We would like to highlight the following global needs: • to make each compound available in all member states • to set-up a prospective evaluation of the Pharmacology of anticancer drugs in children younger than one year of age • to set-up a prospective evaluation of drug related long term effects in survivors	Agreed. General need for availability in all Member States included in the list.
The drugs included in the PEG list are likely to comply with the generally recognised needs for the above cited(*not cited here) conditions. However, our experts suggest that also other substances have to be considered, because they are already of current use as it emerges from some paediatric clinical trials, as the following ones: • Busulphan • Imatinib mesylate • Teniposide • 13-cis-retinoic acid • All-trans-retinoic acid • Monoclonal antibody anti-GD2 • Thalidomide • Melatonyn • Cyclosporin A	Some of the medicinal products already included in the list of paediatric needs oncology part II. See also comment above.

In general, all products authorised by the EMEA in the last 10 years well represent additional innovative existing drugs. It seems appropriate that for all these new drugs the appropriateness of use in children will be investigated. For this reason, some experts have suggested to investigate the appropriateness of use in children of the following products: • Alemtuzumab • Trastuzumab • Aletrinoin • Cladribine (2-CDA) • Arsenic trioxide • Pemetrexed • Bevacizumab • Cetuximab • Celecoxib • Bortezomib • Ibritumomab tiuxetan • Erlotinib • Zoledronic acid	For the time being the PEG considers that these medicinal products are not yet to be included in the list for the following reasons: • **Alemtuzumab**- indication chronic lymphatic leukaemia which is extremely rare in children • T**rastuzumab** - indicated for the treatment of patients with metastatic breast cancer with tumours overexpressing the HER2 protein, which are rare in children • **Alitretinoin** is used as a topical treatment for cutaneous AIDS-related Kaposi's sarcoma in cases when there is no need for oral or intravenous medication. • **Cladribine** - is indicated for the treatment of active Hairy Cell Leukemia which is extremely rare in children • **Arsenic trioxide** –is indicated for induction of remission and consolidation in patients with acute promyelocytic leukemia (APL) who are refractory to, or have relapsed from, retinoid and anthracycline, and whose APL is characterized by the presence of the t(15;17) translocation or PML/RAR-alpha gene expression. • **Pemetrexed** - is indicated for the treatment of patients with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery and the treatment of patients with locally advanced or metastatic non-small cell lung after prior chemotherapy. Both situations are extremely rare in children • **Bevacizumab** - used in combination with intravenous 5-fluorouracil-based chemotherapy, is indicated for first-line treatment of patients with metastatic carcinoma of the colon or rectum. • **Cetuximab** – in combination or as monotherapy for metastatic colorectal carcinoma. • **Celecoxib** –Included in list of paediatric needs rheumatology. • **Bortezomib** - is indicated for the treatment of multiple myeloma patients who have received at least 1 prior therapy. Extremely rare in children • **Ibritumomab tiuxetan** – no data on use in children, currently no identified need. • **Erlotinib** - is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen. Extremely rare in children • **Zoledronic acid** – Treatment with bisphosponates not in the scope of list of paediatric needs chemotherapy part I (chemotherapeutics).

Notwithstanding the agreement on developing new paediatric drugs in this area, some experts are concerned because many drugs in the same clinical category (see individual tumour) are listed in lack of a level of priority indication. This fact could favour the development of both necessary and unnecessary new paediatric drugs, being unnecessary the drugs with the same indication and for which a clinical superiority should not be demonstrated. At this regard our experts' suggestion is that a priority list should be identified on the basis of an approved procedure, in order to concentrate adequate funding and to guarantee optimal clinical trials conduct.	EMEA/PEG procedure for identifying paediatric needs does not include identification of priorities
The group of Experts believe that differences in the age group authorised for using paediatric medicines could favour off-label and inappropriate drugs utilisation. For this reason our experts suggest that a special European Procedure should be applied in order to unify, at an European level and on the basis of the existing clinical evidences, the paediatric uses including the classes of ages for which the drugs are intended. This approach should be agreed both with National Medicines Agencies (through the Coordination Group, ex-Mutual Recognition Facilitation Group-MRFG) and the Sponsors acting in Europe that should be asked to provide the registrative or any other documentation they have at their disposal.	Outside of the task of the EMEA/PEG procedure for identifying paediatric needs. The collection of available data on all existing use of medicinal products in the paediatric population will be covered by the new EU Paediatric regulation (see Article 42, Common position on medicinal products for paediatric use, 10 March 2006.

Additional compounds to be considered: • Bevacizumab: Data on safety, efficacy and PK • Erlotinib: Data on safety, efficacy and PK. Nee for an appropriate oral paediatric formulation • Trofosfamide: Data on safety, efficacy and PK. Need for an appropriate oral paediatric formulation • Cladribine: Data on safety, efficacy and PK in acute meloid leukaemia • Pemetrexed: Data on safety, efficacy and PK • Gemcitabine: Data on safety, efficacy and PK • Cetuximab: Data on safety, efficacy and PK • Trastuzumab: Data on safety, efficacy and PK • Palifermine: Recommendation for dose and use in the paediatric population. Need for evaluation of PK • Altretinoin: Data and literature exist that are likely to provide adequate information for safety and efficacy. Need for a paediatric oral formulation. Need for PK data • Sirolimus: Data on safety, efficacy and PK. Need for an appropriate oral paediatric formulation • Arsenic oxid: Data to define indication and dose in children • Bortezomib: Data on safety, efficacy and PK • Clofarabine: Need to explore new indications and to develop an oral formulation • Imatinib: Need for an appropriate oral paediatric formulation • Dexamethasone: Need to define its indication (ALL, lymphoma) as an anticancer drug. A large literature exists that is likely to provide adequate data to support these indications. • Zoledronic acid: Data on safety, efficacy and PK	Some products already included in the list of paediatric needs oncology part II (supportive therapy) and immunology. See also comments above.
Busulfan: An IV formulation for children should become available.	An iv formulation is available for children of all age groups.
Cladribine: Phase II for relapse AML and ALL in development, very promising. Further studies are desirable.	Indications not approved yet in adults. Full development needed
Tretinoin / Isotretionin: Request for formulation suitable for children Large capsules are impossible for small children to swallow	Agreed.

Add Cardioxane to the list: Desired as protectivum against cardiotoxicity of anthracyclines. Studies to decrease the cardiotoxicity in children are necessary. Furthermore the incidence of secondary tumours should be investigated.	Agreed. To be included in list of paediatric needs oncology part II (supportive therapy)
Glivec: Standard therapy for CML, also in children. Suitable oral formulation is necessary.	Agreed. As Imatinib is already authorised in children > 3 years in the UK, the PEG considers that there is currently no additional need.
Rasburicase: To prevent hyperuricaemia in tumour lysis syndrome. This drug should be available.	Agreed. Rasburicase already available for all paediatric age groups.
Defibrotide On the base of publications from Boston this drug seems to effective in preventing SOS (sinusoidal obstructive syndrome) of the liver. Further investigation desirable.	Included as identified unmet medical need in list of paediatric needs oncology part II (supportive therapy)

Melphalan

Line no.[1] + paragraph no.	Comment and Rationale	Outcome
	We agree with the identified needs. Melphalan is used intravenously in children, at high dose. There is no need for a paediatric oral formulation. Existing data and literature is likely to provide appropriate information.	General comment, noted.
	No interest in identified need for update SPC with PK and other data in AL and Neuroblastoma > 3 months It is mainly used in the conditioning regimen for Haemopoietic Stem Cell (HSC) transplantation in children of all age groups. Meaningful likelihood of a transplant < 3 months of age due to time to transplant since onset of disease and time for unrelated donor search	Disagree. The PEG agreed and considered it important to update the SPC to include existing paediatric data.
	Please add the indication: conditioning for stem cell transplantation	Indication not authorised in children.

Cyclophosphamide

Line no. +	Comment and Rationale	Outcome

[1] Where applicable

para no.		
	We agree with the identified needs. Need for appropriate oral paediatric formulation since cyclophosphamide is being used also as protracted oral administration at low dose. Need for PK evaluation in children younger than 1 year.	Agreed. Included in the list.
	Low priority for PK studies (only). Largely, safely and efficaciously experienced in children of all ages except for PK < 1 yrs of age (but large experience of it at this age as well as in terms of efficacy/safety)	EMEA/PEG procedure for identifying paediatric needs does not include identification of priorities.
	Cyclophosphamide tablets should also be available in smaller mg samples (dividing tablets is not very exact!) - suppositories would be helpful.	Agreed. Need for age appropriate formulation already included in the list
	In future European phase 3 trials for rhabdomyosarcoma daily 25mg/m2 orally will be given. A suitable formulation is therefore necessary so that intervals of 5mg for children up to 1,0 m2 can be given and intervals of 10 mg for bigger children.	Agreed. Need for age appropriate formulation already included in the list
Chlorambucil		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Chorambucil is used in nephrotic syndrom, and rarely in lymphoma in children. This concerns very few patients, and very rarely before the age of 3. Thus, no major needs are identified.	Disagreed. The PEG consideres the availability in all Member States and data on long-term safety and availability of an age appropriate formulation of importance.
Actinomycin D		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	We agree with the identified needs. A large literature exists that is likely to provide adequate data on efficacy and safety. Need for additional prospective evaluation of PK, especially in the young patients (below 1 year)	General comment, noted.

Authorised age group	Low priority for identified need on lower age group definition. Largely, safely and efficaciously experienced in children of all ages with Wilms tumour, RMS, Ewing sarcoma, osteosarcoma (*). PK in children < 1yrs of age advisable	EMEA/PEG procedure for identifying paediatric needs does not include identification of priorities.
Authorised age group	> 6 month (Spain)	Noted. List amended accordingly.
Ifosfamide		
Line no. + para no.	**Comment and Rationale**	**Outcome**
Needs:	Agree with defined needs. A large literature exists that is likely to provide adequate data on efficacy and safety. Need for evaluation of long-term effects.	General comment, noted.
Needs:	Low priority for identified need on lower age group definition. Largely, safely and efficaciously experienced in children of all ages with different solid tumours. Possible role in ALL	EMEA/PEG procedure for identifying paediatric needs does not include identification of priorities
Dacarbazine		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	We agree with the identified needs. A large literature exists that is likely to provide adequate data on efficacy and safety.	General comment, noted.
	No interest in identified need for lower age group definition based on efficacy, safety. Use limited to Hodgkin Disease (HD) of 0-18 yrs of age. HD is exceptional in younger children	EMEA/PEG procedure for identifying paediatric needs does not include identification of priorities
Temozolomide		
Line no. + para no.	**Comment and Rationale**	Outcome
	We agree with the identified needs. There is an urgent need for an appropriate oral pediatric formulation. Additional data on efficacy and safety are needed below the age of	General comment, noted. Needs already included in the needs as identified by the PEG.

	three, but also in older patients to evaluate temozolomide in new indications such as brain tumours other than glial tumours, neuroblastoma, ewing tumours, sarcomas.	
	High priority for identified need for data for efficacy and safety in children < 3 years. It is of great interest in refractory solid tumours other than brain tumours in all paediatric ages	EMEA/PEG procedure for identifying paediatric needs does not include identification of priorities
	Temozolamide, again capsules very hard to swallow for children with brain tumours, some of whom may have swallowing difficulties due to their underlying condition.	Agreed, need for age appropriate formulation already included in the list.
Carmustine		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	We agree with the identified needs. A large literature exists that is likely to provide adequate data. The use of carmustine is contra-indicated under the age of 2 in some member states such as France.	Noted.
Lomustine		
Line no. + para no.	**Comment and Rationale**	Outcome
	We agree with the identified needs. Lomustine is used in particular in lymphoma and medulloblastoma. Need for appropriate oral pediatric formulation.	Noted. Need for age appropriate formulation already included in the list.
	No interest in identified need for efficacy, safety in not-studied ages. Use limited to medulloblastoma > 3 yrs of age. No use expected for children < 3yrs of age so far	Noted. Need for definition of lower age limit already included in the list.
Cisplatin		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	We agree with the identified needs. A large literature exists that is likely to provide adequate information.	General comment, noted.

	Low priority for identified need for efficacy, safety data in not-studied tumour types Largely, safely and efficaciously experienced in children of all ages with many different tumour types. New indications concern refractory/relapsed Hodgkin (HD) and non Hodgkin lymphomas (NHL)	EMEA/PEG procedure for identifying paediatric needs does not include identification of priorities
Carboplatin		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	We agree with the identified needs. A large literature exists that is likely to provide adequate information.	General comment, noted.
	Low priority for identified need for efficacy, safety data in not studied tumour types. Largely, safely and efficaciously experienced in children of all ages with many different tumour types. New indications concern refractory/relapsed Hodgkin and non Hodgkin lymphomas	EMEA/PEG procedure for identifying paediatric needs does not include identification of priorities
Authorised age group	Children (Spain)	Noted. List amended accordingly.
Oxaliplatin		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	We agree with the identified needs. There is a need for prospective evaluation, including PK.	Noted. Need already included in the list
	High priority for identified need for efficacy, safety data in not studied tomour types. Anecdotal experience of the drug in all paediatric ages, but of potential interest in many paediatric solid tumours	EMEA/PEG procedure for identifying paediatric needs does not include identification of priorities
Bleomycin		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	We agree with the identified needs.	Noted.

	Literature contains data that may adequately answer the request. Particular attention should be drawn on lung toxicity in children.	
	No interest in identified need for lower age group definition based on safety, efficacy in not-studied ages. Use limited to HD, germinal and non germinal tumours of 0-18 yrs of age	Disagreed. The PEG considers that there is a need to define the lower age limit and to investigate efficacy and safety where needed.
Methotrexate		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	We agree with the identified needs. Need for appropriate oral paediatric formulation and prospective PK evaluation in the very young patients. Additional data should be provided on leucovorin (appropraite dose and PK), used as rescue after high-dose methotrexate.	Noted. Need already included in the list.
	No interest in identified need for lower age group definition based on efficacy, safety in infants < 6 months. Largely, safely and efficaciously experienced in children of all ages with different tumour types	Disagreed. The PEG considers that there is a need for data on PK, efficacy and safety in infants below 6 months and to specifiy the lower age limit. Additionally, the EMEA/PEG procedure for identifying paediatric needs does not include identification of priorities
	Methotrexate used in the treatment of acute lymphoblastic leukaemia. Although a variety of tablet sizes is available and allows dosing flexibility, these can sometimes lead to potentially dangerous mixtures of prescribed tablet sizes or children being required to swallow large quantities of a single tablet size.	Agreed, need for age appropriate formulation already included in the list.
Thiotepa		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	We agree with the identified needs. Thiotepa is used at high dose before autologous or allogeneic stem cell transplantation.	Noted.
	High priority for identified need PK, efficacy, safety < 12 years in neuroblastoma and brain tumours.Use limited so far to the HSC	EMEA/PEG procedure for identifying paediatric needs does not include identification of priorities

	transplantation setting in all paediatric ages, but no PK study available in all paediatric ages. Drug of interest not only in the HSC transplantation setting	
Fludarabine		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	We agree with the identified needs. In addition, need for data on CNS distribution.	Agreed. Need for data on PK in children already included in the list
	High priority for identified need PK, efficacy, safety < 18 years for relapsed leukemia, allogeneic stem cell transplantation. Use limited so far to the HSC transplantation setting in all paediatric ages, but of interest also in relapsed leukemia in all paediatric ages; PK already available in children	EMEA/PEG procedure for identifying paediatric needs does not include identification of priorities
	Is also used in phase 3 trials for primary AML, not only for relapse.	Noted.
Mercaptopurine		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	We agree with the identified needs. In addition, there is a need for an appropriate oral paediatric formulation. Several pharmacogenetic studies have addressed the value of TPMT genotype. They may provide adequate information.	Noted. Need for age appropriate formulation already included in the list.
	No interest in identified need for pharmacogenetic data (TPMT genotype value). Genetic variation in response (polymorphisms) is already consistently evaluated	Disagreed. The PEG considers the need for pharmacogenetic data to be of importance.
	No interest in identified need on lower age group definition. Largely, safely and efficaciously experienced in children of all ages with ALL, NHD and Langerhans cell tumour.	Disagree. The PEG considers that there is still a need to define the lower age group based on efficacy and safety.
	Mercaptopurine tablets should also be offered in smaller mg rates as well as for Thioguanine tablets.	Noted. Need for age appropriate formulation already included in the list.
	Formulation suitable for children is absolutely necessary for ALL therapy. Dosing schedules with intervals of 5 or 10 mg must be	Agreed. Need for age appropriate formulation already included in the list.

	possible. This is a big daily problem in paediatric oncology.	
Thioguanine		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Adequate oral paediatric formulaton is needed. Data on safety, especially liver toxicity need to be reviewed.	Agreed. Need for age-appropriate formulation and safety data already included in the list.
	No interest in identified need for pharmacogenetic data (TPMT genotype value). Genetic variation in response (polymorphisms) is already consistently evaluated	Disagreed. The PEG considers the need for pharmacogenetic data to be of importance.
	No interest in identified need on lower age group definition. Largely, safely and efficaciously experienced in children of all ages with ALL and NHD	Disagreed. The PEG considers that there is still a need to define the lower age limit based on data on efficacy and safety.
Cytarabine		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	A large literature exists that is likely to provide the required information.	Noted.
	No interest in identified need for efficacy, safety < 3 years. Largely, safely and efficaciously experienced in children of all ages with ALL, AnLL, N	Disagreed. The PEG considers that there is still a need for data on efficacy and safety in children from birth to 3 years.
Liposomal Cytarabine		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	High priority for identified need for PK, efficacy, safety < 18 years Little experience of the drug in all paediatric ages, but of interest in neoplastic meningitis	EMEA/PEG procedure for identifying paediatric needs does not include identification of priorities
5-fluorouracile		
Line no. + para no.	**Comment and Rationale**	**Outcome**

	5-FU is very rarely used in children.	Disagreed. The PEG considers that there is still a need define the potential effect on various responsive tumours in children and where appropriate to study its efficacy and safety.
	No interest in identified need for safety, efficacy in not-studied tumour types. Little interest so far of an old drug little used except for its specific indication (nasopharyngeal carcinoma, hepatocellular carcinoma). PK is not known	Disagreed. The PEG considers that there is still a need to define the potential effect on various responsive tumours in children and where appropriate to study its efficacy and safety.
Capecitabine		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Considering the lack of activity of 5-FU in paediatric malignancies, this is not a priority.	EMEA/PEG procedure for identifying paediatric needs does not include identification of priorities.
	No interest for identified need for efficacy, safety in not studied tumour types. As for 5-Fluorouracil, of which is a precursor	EMEA/PEG procedure for identifying paediatric needs does not include identification of priorities.
Doxorubicin		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	We agree with the identified needs. A large literature exists that is likely to provide adequate information on efficacy and safety. There is a need fro evaluation of PK below the age of one. The role and place of cardioprotective agents need to be adequately addressed in the entire paediatric population.	General comment, noted.
	Low priority for identified need for efficacy, safety in not-studied ages (including newborns). Safely and efficaciously experienced in children of all ages with different tumour types	EMEA/PEG procedure for identifying paediatric needs does not include identification of priorities
	Low priority for identified need on lower age group definition. Safely and efficaciously experienced in children of all ages with different tumour types. Some toxicity expected in lower ages.	EMEA/PEG procedure for identifying paediatric needs does not include identification of priorities.
Liposomal Doxorubicin		

Line no. + para no.	Comment and Rationale	Outcome
	We agree with the identified needs. With a special attention of cardiac toxicity.	General comment, noted.
	High priority for identified need for efficacy, safety in not-studied ages. Little experience in all paediatric ages, but of interest in many types of paediatric tumours	EMEA/PEG procedure for identifying paediatric needs does not include identification of priorities
Daunorubicin		
Line no. + para no.	**Comment and Rationale**	Outcome
	We agree with the identified needs. A large literature exists that is likely to provide adequate information on efficacy and safety. There is a need fro evaluation of PK below the age of one. The role and place of cardioprotective agents need to be adequately addressed in the entire paediatric population.	General comment, noted.
	Low priority for identified need for efficacy, safety in not-studied ages (including newborns). Safely and efficaciously experienced in children of all ages with different tumour types	EMEA/PEG procedure for identifying paediatric needs does not include identification of priorities
	Low priority for identified need on lower age group definition. Safely and efficaciously experienced in children of all ages with different tumour types. Some toxicity expected in lower ages	EMEA/PEG procedure for identifying paediatric needs does not include identification of priorities
Liposomal Daunorubicin		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Data on efficacy and safety in same indications as doxorubicin and daunorubcin, with a special attention on cardiac toxicity	Noted.
Epirubicin		
Line no. + para no.	**Comment and Rationale**	**Outcome**

	We agree with the identified needs. A large literature exists that is likely to provide adequate information on efficacy and safety. There is a need for evaluation of PK below the age of one. The role and place of cardioprotective agents need to be adequately addressed in the entire paediatric population.	General comment, noted.
	No interest in identified need for data on safety, efficacy in not-studied tumour types. New molecules of the anthracyclines family appear to be more efficacious and less toxic. Little interest for future use in different tumour types	General comment, noted.
Idarubicin		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	We agree with the identified needs. In addition, there is a need for appropriate oral paediatric formulation. Need for evaluation of PK below the age of 1. The role and place of cardioprotective agents need to be adequately addressed in the entire paediatric population.	Agreed. Need for age-appropriate formulation added to the list.
	Low priority for identified need for efficacy, safety in not-studied ages. Largely, safely and efficaciously experienced in children of all ages with AML, ALL	EMEA/PEG procedure for identifying paediatric needs does not include identification of priorities
	Low priority for identified need on lower age group definition. Safely and efficaciously experienced in children of all ages with different tumour types. Some toxicity expected in lower ages	EMEA/PEG procedure for identifying paediatric needs does not include identification of priorities
	Request for studies concerning the aequitoxic doses of several anthracyclines to compare the cardiotoxicity between the combinations with different anthracyclines.	Noted. EMEA/PEG procedure for identifying paediatric needs does not include specifications on requested studies.
Mitoxantrone		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Mitoxantrone is used IV only.	Noted.
	No interest in identified need for efficacy and safety data. Already experienced in children with AnLL aged 0-18 yrs	Agreed. Authorised in Spain > 0 years, no additional need for PK,

		efficacy and safety data in children < 3 years.
Authorised age group	> 0 years (Spain)	Noted. List amended accordingly.
Etoposide		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	We agree with the identified needs. There is a large literature that is likely to provide adequate information on efficacy and safety. There is a need for an appropriate oral paediatric formulation.	General comment, noted.
	No interest in identified need for data on safety, efficacy in not-studied tumour types. Largely, safely and efficaciously experienced in children of all ages with many different tumour types. New indications are not expected	Disagreed. The PEG considers that there is still a need for to define the potential effect of the product on various responsive tumours in children.
	Request for suitable paediatric formulations.	Agreed. Need already included in the list.
Etopophos		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Recommendation for dose and use in the paediatric population.	Noted. Rarely used in children. No need identified.
Vincristine		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	We agree with the identified needs. Literature is likely to provide adequate information on safety and efficacy. Additional information on PK below the age of one is needed.	General comment, noted.
	No interest in identified need for lower age group definition based on efficacy, safety data in not studied areas. Largely, safely and efficaciously experienced in children of all ages with different tumour types	Disagreed. The PEG considers that there is still a need to define the lower age limit

Vinblastine		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	We agree with the identified needs. Literature is likely to provide adequate information on safety and efficacy. Additional information on PK below the age of one is needed.	General comment, noted.
	Low priority for identified need for lower age group definition based on efficacy, safety data in not-studied ages. Large experience in HD. Additional indication in Langherhans cells tumour and acute large cell lymphoma (ALCL) of 0-18 years of age.	EMEA/PEG procedure for identifying paediatric needs does not include identification of priorities
	Low priority for identified need for data on safety, efficacy in brain tumours. Little experience of the drug in brain tumours, but already included in clinical trials for HD and Langherans cells tumour	EMEA/PEG procedure for identifying paediatric needs does not include identification of priorities
	Use limited to HD and Langerhans cells tumour (new indication) of 0-18 yrs of age	Noted.
Authorised age group	> 0 years (Spain)	Noted. List amended accordingly.

Vindesine		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	We agree with the identified needs. Literature is likely to provide adequate information on safety and efficacy. Additional information on PK below the age of one is needed.	General comment, noted.
	Low priority for identified need for efficacy, safety in not-studied ages. Recent experience in NHD and ALL of 0-18 years	EMEA/PEG procedure for identifying paediatric needs does not include identification of priorities
	No interest in identified need for data on safety, efficacy in not-studied tumour types. Large experience in NHL and relapsed ALL. No experience in other paediatric tumours, but likely of little interest	Disagreed. The PEG considers that there is a need for data on safety, efficacy in not-studied tumour types and to define the lower age limit..

	No interest in identified need on lower age group definition. Use limited to NHL and ALL in children of 0-18 yrs of age	Disagreed. See comment above.
Vinorelbine		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Need for data on safety, efficacy and PK for both the IV and the oral form. Appropriate oral paediatric formulation will be needed.	The PEG did not identify a need for Vinorelbine. Not included in the list.
Paclitaxel		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	We agree with the identified needs. With a special attention on toxicity of solvents in relation with schedule of administration.	General comment, noted.
	High priority for identified need for data on safety, efficacy in not-studied tumour types. Some phase I and II studies in the literature justify a real interest for paediatric tumours of this new family of drugs. No data concerning paediatric ages	EMEA/PEG procedure for identifying paediatric needs does not include identification of priorities
L-Asparaginase / PEG-Asparaginase		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	We agree with the identified needs. Need for availability of Erwiniase, as well.	Agreed. Erwiniase included in the list.
	Guarantee of the supplying is essential. Recently some problems arise. Several forms of asparaginase differ in kinetics, dosing and dose-intervals. Studies are necessary to develop the optimal therapy, also in cases of an allergy against the primary form.	Agreed.
Procarbazine		
Line no. +	**Comment and Rationale**	**Outcome**

para no.		
	We agree with the identified needs. Need for an appropriate oral paediatric formulation.	Noted. Need for age appropriate formulation added to the list.
	No interest in identified need on lower age group definition.Use limited to HD in children of 0-18 yrs of age. HD is exceptional in younger children.	Disagreed. The PEG considers that there is still a need to define the lower age limit based on data on efficacy and safety.
	No interest in identified need for efficacy, safety in not studied ages. Use limited to HD in children of 0-18 years of age.	Disagreed. See comment above.
Irinotecan		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	High priority for identified need for data on safety, efficacy in not-studied tumour types. Largely experienced drug in children of all ages with different relapsed/refractory tumour types. Not yet included in front line trials	EMEA/PEG procedure for identifying paediatric needs does not include identification of priorities
Topotecan		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	High priority for identified need for data on safety, efficacy in not-studied tumour types. Some interesting experience in children of all ages with different relapsed/refractory tumour types. Not yet included in front line trials	Included in the list. PEG Paediatric Needs Assessment Procedure does not set priorities.
Docetaxel		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	High priority for identified need for data on safety, efficacy in not-studied tumour types. Some phase I and II studies in the literature justify a real interest for paediatric tumours of this new family of drugs. No data concerning paediatric ages	EMEA/PEG procedure for identifying paediatric needs does not include identification of priorities. Need already included in the list.

Rituximab		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	High priority for identified need for data on safety, efficacy, PK < 19 yrs in CD20+ NHL. It is of interest for specific indications (CD20+ ALL and NHL) in all paediatric ages, but no PK and efficacy/safety studies are known so far. Role in front line therapy as well as in intensification protocols (autologous HSC transplantation)	EMEA/PEG procedure for identifying paediatric needs does not include identification of priorities.
	Additional indications are: severe autoimmune hemolytic anaemia and refractory ITP.	Noted.
ATRA (all trans retinoic acid)		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	ATRA (all trans retinoic acid) used in the treatment of acute promyelocytic leukaemia, where large capsules are impossible for younger children to swallow.	Noted. PML is extremely rare in children, see comments above.
Cis retinoic acid (isotretinoin)		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	cis retinoic acid (isotretinoin) for Neuroblastoma: the large capsules are impossible for small children to swallow.	Agreed. Added to the list. Need for extension of the indication to neuroblastoma