



European Medicines Agency

SUBMISSION OF COMMENTS ON

PRIORITY-LIST OF OFF-PATENT MEDICINAL PRODUCTS FOR PAEDIATRIC STUDIES/Doc. Ref.EMA/496777/2006

COMMENTS FROM SIOP Europe and TEDDY Therapeutic Expert Group in Oncology

GENERAL COMMENTS

SIOP Europe represents an established network of experts in clinical trials and management of children with cancer. We have many decades of experience of the safety and efficacy of 'off-label' use of anti-cancer drugs in children, both within and outside of clinical trials.

The TEDDY network of excellence set up an *ad hoc* Therapeutic Expert Group in Oncology in December 2005. This comprises experts who are actively working in the field of paediatric oncology. The work of the TEDDY project led to the submission of a detailed report to the EMA paediatric expert group (submitted by May 31st 2006). This has subsequently been modified following a joint meeting of SIOP Europe and TEDDY experts in November 2006, to discuss the needs and priorities to fully evaluate off-patent drugs commonly used in paediatric cancer (attached as Annex 2 TEDDY & SIOPE).

The experts of the joint SIOP E/TEDDY group are very supportive of the initiative represented by the publication of this list, to improve the knowledge base of paediatric use of such drugs. We are committed to working together to prioritise drugs that need further research in paediatrics and to facilitate trials that can address these needs. Based on our experience, we would like to propose that this list is enlarged to include other substances of paediatric interest that are commonly used in a high proportion of children with cancer.

Please see our covering letter for further details.

SPECIFIC COMMENTS ON TEXT

Public

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 85 95
E-mail: mail@emea.eu.int <http://www.emea.eu.int>

©EMA 2005 Reproduction and/or distribution of this document is authorised for non-commercial purposes only provided the EMA is acknowledged

GUIDELINE SECTION TITLE		
Line no ¹ . + paragraph no.	Comment and Rationale	Proposed change (if applicable)
Solid tumours and other cancers Cyclophosphamide Specific Needs: Oral Formulation	<p>We agree with the need for an appropriate oral pediatric formulation since cyclophosphamide is being used as a protracted oral administration at low dose. However, the needs are broader than this. There is a need for PK evaluation at all doses in young children and PK evaluation of high dose cyclophosphamide across the entire paediatric age range since it is widely used in stem cell transplantation.</p>	<p>Add: PK studies in young children (age < 3 yrs) and when used at high dose at all ages.</p>
Solid tumours and other cancers Vinblastine, Vincristine, Specific needs: none stated Additional drugs to be considered in this category Vinorelbine Vindesine	<p>We agree that this family of drugs needs to be studied in a wider age range and indications. Existing literature and ongoing studies are likely to provide adequate information on safety and efficacy except for rarer indications (e.g. Langerhan's cell histiocytosis, large cell anaplastic lymphoma). There is a need for PK studies in young children.</p>	<p>Add: PK studies in young children (age < 3yrs).</p> <p>Efficacy studies in rare indications (vinblastine for LCH, large cell anaplastic lymphoma) across all ages 0-18 yrs.</p> <p>An oral formulation of vinorelbine will be required – it is now being used in 'maintenance therapy' of high risk soft tissue sarcomas, which may affect infants and young children.</p>
Solid tumours and other cancers Etoposide Specific needs: oral formulation Additional drug to be considered in	<p>We agree with the need for an oral formulation. This drug is commonly used in a protracted oral schedule in palliative chemotherapy, often with great benefit.</p>	<p>Add: PK studies in young (< 3 yrs)/light (< 12 Kg) children.</p> <p>Need for PK studies of high dose therapy with etoposide</p> <p>Need for PK and safety/efficacy studies of etoposide to determine its indications and appropriate dose-schedule in the paediatric population.</p>

¹ Where available

<p>this category:</p> <p>Etopophos</p>		
<p>Solid tumours and other cancers Cisplatin, Carboplatin Specific needs: none stated</p>	<p>These drugs are commonly used across a wide range of paediatric tumours, especially those affecting very young children (hepatoblastoma, brain tumours, neuroblastoma). There are ongoing PK studies that may provide sufficient data on use at standard doses. There is a need for further evaluation of high dose carboplatin in infants, who are currently dosed per Kg. New indications concern refractory/relapsed Hodgkin (HD) and non Hodgkin lymphomas (NHL).</p>	<p>There is a body of literature and ongoing PK studies that may provide sufficient data on use at standard doses.</p> <p>Add: PK studies of high dose carboplatin in infants</p>
<p>Solid tumours and other cancers Doxorubicin Daunorubicin Epirubicin Idarubicin Liposomal doxorubicin Liposomal daunorubicin</p>	<p>The anthracycline drugs need to be reinstated in the priority list. Existing literature is likely to provide adequate information on safety and efficacy. However, there is a need for PK studies of the huge variety of dose and schedules currently used in paediatrics, particularly in very young children. The role of concomitant administration with cardio-protectants needs to be evaluated for their effects on PK in the paediatric age range.</p>	<p>Include the commonly used anthracycline drugs in the priority list.</p> <p>Need for PK studies of widely differing schedules of administration and in younger age groups, including the newborn. Need for studies evaluating predictive markers for cardiac toxicity and impact of combination with cardio-protectants.</p>
<p>Solid tumours and other cancers Actinomycin D</p>	<p>Actinomycin D needs to be reinstated in the priority list. Although it has been used for over 40 years in the treatment of Wilms tumour and soft tissue sarcomas, there are insufficient data on its safety and efficacy in very young children, including the newborn, who may require it. Life threatening hepatotoxicity continues to be seen in contemporary clinical trials for Wilms and soft tissue sarcoma. There are inconsistent recommendations for dose modification by age/weight according to clinical trial protocol, due to lack of evidence in this very young patient population.</p>	<p>Include Actinomycin D in the priority list.</p> <p>Need for PK studies of the different dose recommendations in younger age groups (< 1yr or < 12 Kg).</p>

Irinotecan	Reasonable experience of use of this drug in children of all ages with different relapsed/refractory tumour types. Not yet included in front line trials.	Include irinotecan in the priority list. A substantial body of existing literature and ongoing studies should provide PK data. Need for efficacy and safety studies to define role in childhood solid tumours.
Fludarabine	Increasingly used in treatment of relapsed leukaemia/lymphoma and as conditioning in 'mini-transplants'.	Include fludarabine in the priority list. Need for PK, safety and efficacy studies in appropriate indications. Need for data on penetration of the central nervous system.
Solid tumours and other cancers Lomustine Specific needs: formulation. Carmustine, 5-fluorouracil Hydroxycarbamide	Carmustine, lomustine and 5-fluorouracil are still mentioned in the list despite being assigned a low priority for investigation, according to the Experts, as pointed out in the TEDDY report (May 31st 2006); Lomustine (CCNU) is commonly used in some childhood brain tumours and there is a formulation issue for young children. Carmustine (BCNU) is rarely used as conditioning for high dose therapy for relapsed lymphomas.	Retain need for formulation of Lomustine (CCNU). Do not include carmustine, 5-fluorouracil and hydroxycarbamide in the priority list
Additional drugs to be considered in this category: Cytarabine Ifosfamide	Cytarabine: largely, safely and efficaciously experienced in children of all ages with ALL, AnLL, NHL. Ifosfamide: largely, safely and efficaciously experienced in children of all ages with different solid tumours. Possible role in ALL.	Need for efficacy/safety studies in children <3 yrs Need to define lower age group.
Additional drugs to be considered in this category: Thiotepa	Thiotepa: use limited so far to the HSC 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. Paclitaxel: some phase I and II studies in the literature justify a	Need for PK/efficacy/safety studies in children <12 yrs with neuroblastoma and brain tumours

Paclitaxel	real interest for paediatric tumours of this new family of drugs.	Need for PKstudies in all age groups
Methotrexate Mercaptopurine	Largely, safely and efficaciously experienced in children of all ages with different tumours.	Need of PK/efficacy/safety studies in not-studied tumours type Need of appropriate oral formulations in all age groups

Please feel free to add more rows if needed.

These comments and the identity of the sender will be published on the EMEA website unless a specific justified objection was received by EMEA.

List of SIOPEurope and TEDDY experts who contributed to these comments

Name	Institution
Organisers of the joint SIOPE-TEDDY meeting	
Andrea Biondi	President of SIOPEurope, Università degli Studi di Milano – Bicocca, Italy
Kathy Pritchard-Jones	Chairman, SIOPEurope Clinical Trials Committee. Institute of Cancer Research and Royal Marsden Hospital, Sutton, UK
Gilles Vassal	ITCC, Institut Gustav Roussy, Villejuif, France
Alan Boddy	Chairman of the Children's Cancer and Leukaemia Pharmacology Working Group, University of Newcastle, UK
Paolo Paolucci	TEDDY TEG Oncology, Modena, Italy
Other Contributors	
Stein Bergan	Rikshospitalet Hege Thoresen - Universitetet I, Oslo, Norway
Gianni Bisogno	Clinica Oncoematologica Pediatrica, Padova, Italy
Mariana Catapano	Consorzio per Valutazioni Biologiche e Farmacologiche, Italy
Bettina Couderc	Institut Claudius Regaud, Toulouse, France
Deirdre Dodd	University of Newcastle, Newcastle, UK
Carlo Giaquinto	Azienda Ospedaliera di Padova and TEDDY, Padova, Italy
Georg Hempel	Universität Münster, Münster, Germany
Achille Iolascon	Università degli Studi di Napoli, Napoli, Italy
Evelyne Jacqz-Aigrain	Hôpital Robert Debré, France

Pamela Kearns	Institute for Child Life and Health, Bristol, UK
Elke Krekels	Universiteit Leiden, Leiden, The Netherlands
Stephanie Natsch	University Medical Centre, Nijmegen, The Netherlands
Angelo Paci	Institut de cancérologie Gustave Roussy, Paris, France
Mario Ragazzi	Università degli Studi di Pavia, Pavia, Italy
Maroeska te Loo	University Medical Centre, Nijmegen, The Netherlands
Annalisa Trama	Istituto Superiore di Sanità, Sanita, Italy