14 June 2009

The

SUBMISSION OF COMMENTS ON

Update of the Priority List of off-patent medicines for children

COMMENTS FROM:

The following contribution to the revision of the EMEA priority list of off-patent medicines in the field of Pediatric Oncology has been prepared jointly by SIOPEurope (Chair: Kathy Pritchard Jones), IBFM (Chair: Martin Schrappe) and ITCC (Chair: Gilles Vassal).

Methodology.

Information on the revision process has been sent to the chairs of each European Tumor groups, along with previous comments made by ITCC and SIOPeurope on the previous version of the priority list. Each chair was asked to make comments and to identify the specific paediatric needs for off patent drugs currently used in the treatment of the disease there are in charge of..

Specific contributions have been made by:

- Christina Peters for the EBMT Paediatric Diseases Working Party
- Peter Bader for the Stem cell transplantation I-BFM group
- Andrea Biondi for the I-BFM group
- François Doz and David Walker for the SIOPE Brain tumour group
- Norbert Graf for the SIOP – Renal tumour study group
- Adele Canete for the SIOPE Neuroblastoma group (SIOPEN)
- Piotr Czauderna for the SIOPEL (Hepatoblastoma) group
- Gianni Bisogno for the EpSSG (Soft tissue sarcoma group)
- Ian Lewis for the Euro-Ewing group

Results

The identified needs for off-patent oncology drugs can be summarized in 5 topics:

1. chemotherapy in children below the age of 3, and especially in infants
   needs for relevant pharmacological data to define safe and effective use in young children
2. age- appropriate formulation for oral oncology products
   13-cis retinoic acid, etoposide, vinorelbine
3. long-term sequellae in survivors of childhood cancer
4. development of CNS-directed chemotherapy with cytotoxic agents through the intrathecal route
   it is anticipated that incidence of leptomenigeal disease will rise as more effective systemic therapies are introduced
5. pharmacokinetics of current cytotoxic drugs in extreme situation (single kidney, obese patients, …) where therapeutic monitoring should be considered
   carboplatin, etoposide, ifosfamide, …..

The following table provides details drug by drug on anticancer drugs as well as supportive care drugs, in particular those used in the hematopoietic stem cell transplantation setting.

Comments on the existing list (EMEA/226983/2008 29 august 2008)

The Pediatric Oncology community would like to highlight that FP7 funded projects are currently addressing the following needs:

- temozolomide – age appropriate formulation and PK in children
- doxorubicin – PK in young children
- cyclophosphamide – age appropriate formulation and PK of metabolites in children
- 6-mercaptopurine – age appropriate formulation

On the other hand, the needs displayed in the priority list for the following drugs are endorsed:

Actinomycin, asparaginase, cladribine, daunorubicin, cytarabin, topotecan

2. SPECIFIC COMMENTS ON TEXT

Line No of the first line(s) affected. <*e.g. Line 20-23*>	**Stakeholder No.** <*to be completed by EMEA*>	**Comment and Rationale; proposed changes** <*if changes to the wording are suggested, they should be highlighted using "track changes"*>	**Outcome** <*to be completed by EMEA*>
13-cis-retinoic acid		**Indication** Minimal residual disease in high risk neuroblastoma after high-dose chemotherapy and autologous stem cell transplantation **Specific needs** Age- appropriate oral formulation	
Ifosfamide		**Comments:** Indication – bone and soft-tissue sarcomas, nephroblastoma, lymphoma **Proposed change (if any):** Need for PK data in children with a single kidney. Long term follow-up of kidney function and evaluation of other long –term sequellae	
Carboplatin		**Comments:** Indication – neuroblastoma, nephroblastoma, CNS, germ cell tumor, hepatoblastoma, retinoblastoma, Hodgkin, soft-tissue sarcoma **Proposed change (if any):** PK in infants PK in children with single kidneys. Long term follow-up of kidney function in combination with ifosfamide.	

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Etoposide		**Comments:** Indication – neuroblastoma, CNS tumours, Germ cell tumours, leukemia, lymphoma, retinoblastoma, bone and soft tissue sarcomas **Proposed change (if any):** Age-appropriate formulation for oral use Data on intrathecal use for leptomeningeal disease PK in infants PK in children with a single kidney	
Vincristin		**Comments:** Patients > 10 years of age develop more often neurotoxicity. PK data and pharmacogenomics need to be addressed.	
Vinorelbine		**Condition** Soft tissue sarcoma **Specific needs** Data on PK, efficacy and safety Age-appropriate oral formulation	
Topotecan		**Condition** Sarcomas, neuroblastoma	

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		Specific needs Age appropriate oral formulation	
Alemtuzumab		**Comments:** Conditions: rejection prophylaxis and graft versus Host Disease Prophylaxis (GVHD) in patients undergoing unrelated donor transplantation or transplantation from HLA-mismatched family donors for malignant and non-malignant diseases. **Specific Needs:** Data on efficacy and safety in all age groups.	
ATG Fresenius		**Comments:** Conditions: Anti Thymocyte Globuline F is widely used to prevent rejection and GVHD. It has a different mode of action compared to Alemtuzumab, e.g. shorter time of immunosuppression and therefore preferably used in patients with acute leukemia. **Specific Needs:** Data on efficacy and safety in all age groups.	
ATG Genzyme		**Comments:** Conditions: GVHD- and rejection prophylaxis for children before HLA mismatched or unrelated HSCT. Severe Aplastic Anaemia: first line therap y **Specific needs:**	

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		Data on efficacy and safety. A randomized trial between ATG F and ATG G would help to clarify the specific efficiency within the different conditions	
Cyclophosphamide		**Conditions:** High dose (120-200 mg/kg) before allo and auto HSCT: Acute lymphoblastic Leukemia, acute myeloid leukemia, juvenile myelomonocytic leukemia, myelodysplastic syndrome, Non Hodgkin Lymphoma, Solid tumours, Severe aplastic Anaemia, Severe combined immunodeficiency **Specific needs**: Data on long term/late effects	
Fludarabine		**Conditions** High dose (120-200 mg/m2) before allo HSCT: All types of acute and chronic leukemia, Non malignant diseases: Severe Immunodeficiencies, Red Cell disorders (e.g. thalasaemia, sickle cell disease, metabolic disorders (e.g. adrenoleukodystrophy, mucopolysaccharidosis etc.) **Specific needs:** PK-data, efficacy, safety in all paediatric age groups	
Etoposide phosphate		**Conditions:** High dose (40-60 mg/kg) before allo and auto HSCT for Acute lymphoblastic leukemia (ALL), Non Hodgkin Lymphoma, Solid tumours,	

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		Haemophagocytic Lymphohistiocytosis (HLH) **Specific needs:** PK, short and long term safety in all paediatric age groups	
Melphalan		**Conditions:** High dose (140-160 mg/kg) and before allo and auto HSCT for acute and chronic leukaemia, solid tumours, myelodysplastic syndrome, inborn errors of metabolism, red cell disorders, HLH **Specific needs**: PK, short and long term safety (!!!fertility!!!) in all paediatric age groups	
Thiotepa		**Conditions**: Before allo and auto HSCT for acute leukaemia, Non Hodgkin lymphoma, solid tumours, **Specific needs:** PK, efficacy, short and long term safety in all paediatric age groups	
Treosulfan		**Conditions:** High dose (> 36g/m2) : before allo and auto HSCT for acute and chronic leukaemia, solid tumours, myelodysplastic syndrome, inborn errors of metabolism, red cell disorders, HLH. Alternative option for patients with graft failure, relapse and/or organ toxicity to	

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		busulfan or total body irradiation **Specific needs:** PK, efficacy, short and long term safety (!!!fertility!!!) in all paediatric age groups	
Mycophenolic acid		**Conditions:** Short and long term immunosuppression for prevention of graft rejection and GVD after allogeneic HSCT **Specific needs:** Efficacy and short/long term safety	
Tacrolimus		**Conditions:** Short and long term immunosuppression for prevention of graft rejection and GVD after allogeneic HSCT **Specific needs:** PK, efficacy, short/long term safety	
Sirolimus		**Conditions:** Short and long term immunosuppression for prevention of graft rejection and GVD after allogeneic HSCT **Specific needs:** PK, efficacy, short/long term safety	
Ganciclovir		**Conditions:** Prophylaxis and therapy of cytomegalovirus-infection after allogeneic HSCT in	

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		any indication. **Specific needs**: PK, efficacy, safety Age appropriate oral formulation!	
Cidofovir		**Conditions:** Viral infections after allogeneic HSCT, esp. adenovirus-infections **Specific needs:** PK, efficacy, safety	
Ribavirin		Conditions: Viral infections after allogeneic HSCT, esp. adenovirus-infections Specific needs: i.v., oral formulation: PK, efficacy, safety	
Linezolid		Conditions: Bacterial infection (blood, pneumonia, endocarditis etc.) with multiresistant grampositive pathogens during severe neutropenia after allo and auto HSCT Specific needs: PK, efficacy, safety	