European Medicines Agency
Evaluation of Medicines for Human Use

London, 25 September 2006
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OVERVIEW OF COMMENTS RECEIVED ON LIST OF PAEDIATRIC NEEDS IMMUNOLOGY

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

Add name followed by link to individual received comment (upon publication by Web Services)

	Name of Organisation or individual	Country
1	ICCCPO Secretariat (The International Confederation of Childhood Cancer Parent Organisations)	Netherlands
2	Teddy (Task force in Europe for the drug development for the young)	Italy
3	Astellas Pharma GmbH	Germany
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Table 2:Discussion of comments

GENERAL COMMENTS - OVERVIEW	
The drugs included in the PEG list are likely to comply with the generally recognised needs in the paediatric immunology field. However, it is suggested 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: • Fludarabine • Alemtuzumab • Busulfan	Fludarabine, Alemtuzumab, Busulfan, are already covered by the list of paediatric needs chemotherapy (listed with the exception of Alemtuzumab, which is up to now only approved as thirdline therapy in adults for CLL, a disease not relevant in this context)
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 our experts have suggested to investigate the appropriateness of use in children of the following product, currently authorised for adult use and/or few paediatric age groups: • Alemtuzumab (see below) • Busulfan (high priority in bone marrow transplantation 0-18 years) • Mycophenolate mofetil • Sirolimus • Basiliximab • Tacrolimus	• Alemtuzumab (see comment above) • Busulfan originally was to be included in the chemotherapy list, It has been removed from the list, since the PEG considered available information and labelling as sufficient. • Mycophenolate mofetil is authorised > 2 years. The PEG identified a need for data on PK, efficacy and safety in children < 2 years. • Sirolimus: There is a need for extension of the indication. Added to the list: “Based on the mechanism of action, to define the potential effect of the product on various immunology indications.” • Basiliximab: The PEG identified an additional need for extension of the indication to liver and bone marrow transplantation, as well as < 1 year • Tacrolimus: The PEG agrees and identified an additional need for data on PK, efficacy and safety in children < 2 years

Notwithstanding the agreement on developing new paediatric drugs in this area, some experts are concerned because many drugs in the same clinical category 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. Authorisation in minors has been reported restricted to some drugs with significant variability among Countries. 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.
It is suggested to include the following active substance in the list: **Fludarabine** High priority for need to extend the indications in children receiving bone marrow transplantion	*Fludarabine already covered by list of paediatric needs chemotherapy part I.*
It is suggested to include the following active substance in the list: **Alemtuzumab** High priority to extend the indication in children receiving bone marrow transplantation Need for (low priority) for efficacy/safety data in kidney transplantation	*Alemtuzumab* already covered by list of paediatric needs *chemotherapy* part I.
Need to collect as many data as possible about availability of paediatric formulations for these drugs across all Member States.	*See comment above (EU Paediatric Regulation).*

SPECIFIC COMMENTS ON TEXT

Tacrolimus

Line no. + para no.	Comment and Rationale	Outcome
Needs	High priority for need of efficacy/safety studies where appropriate in new indications. Need for efficacy/safety in severe autoimmune diseases of childhood, bone marrow transplantation, and severe atopic dermatitis	Need already covered in identified needs: Based on the mechanism of action, to define the potential effect of the product in various immunology indications (including Bone Marrow Transplantation) and where appropriate study its efficacy and safety
Authorised indication	CHMP/PEG Proposal: Prevention and treatment of rejection in kidney, heart and liver transplants. Proposal for rewording: Prevention of rejection in kidney, heart and liver transplants and treatment of allograft rejection. Comment: The adoption to the harmonized Prograf SPC of the Commission Decision, dated 10 April 2006, as outcome of an article 30 referral procedure for indications should be considered. The indication prevention of rejection is restricted to transplanted kidney, liver and heart, but the indication treatment of allograft rejection is according to the harmonised SPC not restricted to specific solid organs.	Agreed: List amended accordingly: Authorised indication: prophylaxis of transplant rejection in liver, kidney or heart allograft recipients and treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products.
Authorised age group	CHMP/PEG Proposal: >2 years (liver and kidney) Proposal for rewording: Children (age group unspecified) Comment: In Section 4.1 of the harmonized SPC the population (adult or children) is not specified for the indications. The dosage recommendations in Section 4.2 of the harmonized SPC given for children is general, independent from the age group. Therefore we would expect to have an identical statement in the age group specification as the other CNI, ciclosporin: Children (age group	Disagreed. Section 4.2 of the SPC states that limited or no (depending on the indication) data in children, 2 years are available.

	unspecified). Currently there is no rationale for the age limit (>2 years) in children for tacrolimus as provided in the draft paper	
Authorised dose:	CHMP Proposal: Liver, an initial oral dose of 0,30mg/kg per day should be administrated in two divided doses (e.g. morning and evening). Kidney: Doses in children often 1.5-2 times the adult dose Proposal for rewording: Liver and Kidney: An initial oral dose of 0.30 mg/kg per day should be administered in two divided doses (e.g. morning and evening). Heart: Without antibody induction: Initiation int4ravenously at a starting dose 0.03-0.05 mg/kg/day and convert to oral therapy at a starting dose of 0.30 mg/kg/day. Following antibody induction: An initial oral dose of 0.10-0.30 mg/kg/day should be administrated as two divided doses (e.g morning and evening). Maintenance doses in children are often 1.5-2 times adult dose. Comment: The adoption to the harmonized Prograf SPC of the Commission Decision, dated 10 April 2006, as outcome of an article 30 referral procedure for the relevant authorized doses should be considered.	Agreed. List amended accordingly.
Authorised formulation:	CHMP/PEG Proposal: 0.5, 1 mg and 5 mg capsules; 5mg/ml concentrate for dilution of infusion Proposal for rewording: 0.5, 1 mg and 5 mg capsules, hard; 5 mg/ml concentrate for solution for infusion. Comment: The terms for the marketed formulations have been updated during the referral procedure for Prograf to the European standard terms. Therefore the adaption to currently approved terms is recommended.	Agreed. List amended accordingly.
	Add need: High priority to harmonize authorization and define lower age limits in children across Member States	Agreed.
	Change age limit to: all age groups (United Kingdom)	Agreed. See comments above.

Azathioprine		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Low priority for need for efficacy/safety where appropriate in new immunology indications	EMEA/PEG procedure for identifying paediatric needs does not include identification of priorities.
	Suggestion to add need for efficacy/safety in Crohn's diseases and ulcerative colitis. Need to harmonize indication for autoimmune hepatitis across Member States.	Noted. Suggested needs already covered by the needs as identified by the PEG.
	No interest in pharmacogenetic data: not a priority as already consistently evaluated	Agreed. List amended accordingly. (EMEA/PEG procedure for identifying paediatric needs does not include identification of priorities).
	High priority for need for definition of lower age limit, because largely used in children of different ages. Need to define lower age limit for each indication according to available safety/efficacy data	EMEA/PEG procedure for identifying paediatric needs does not include identification of priorities. Need already covered by needs as identified by the PEG.
Mycophenolate mofetil		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	High priority for need for efficacy/safety data where appropriate in new immunology indications	EMEA/PEG procedure for identifying paediatric needs does not include identification of priorities.
	Need for efficacy/safety in severe autoimmune diseases of childhood, steroid-resistant and steroid-dependent nephrotic syndrome, bone marrow transplantation, solid organ transplantation other than kidney, refractory ITP	Noted. Needs already covered by the needs as identified by the PEG.
	It is suggested to add need for: extension of the indication to children < 2 years (low priority)	Agreed. List amended accordingly.

Mycophenolate sodium		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	No priority for extension of the indication in all age groups as there is very little experience with this drug in children (largely substituted by mycophenolate mofetil)	Disagreed. The PEG considers that there is still a need for a age appropriate formulation and an extension of the indication to all age groups.
Sirolimus		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Additional need (low priority) to assess efficacy/safety data in children with severe autoimmune diseases (experience is already available)	Noted. Identified needs already covered by needs identified by the PEG.
	Low priority for need for extension of the indication to all age groups including newborns	EMEA/PEG procedure for identifying paediatric needs does not include identification of priorities.
	Add need to obtain PK data in children (all age groups).	Identified needs already coverec by needs identified by the PEG.
Muronomab-CD3		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Low priority for need for extension of the indication for BMT (dose/efficacy/safety)as conditioning regimen >1 yrs Extension of indication for BMT should not be focused of conditioning regimen, but also to treatment of GvHD	EMEA/PEG procedure for identifying paediatric needs does not include identification of priorities. Agreed. List amended accordingly.
	Change authorised age group to: Children (Spain)	Noted. Information on authorisation status in all Member States not available during PEG paediatric needs assessment procedure. Refer to EMEA/PEG procedure for identifying paediatric needs (Limits of the methodology chosen).

Basiliximab		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Additional need (high priority) for dose/efficacy/safety also in liver and heart transplantation, even in infants <1 yrs and	Agreed. List amended accordingly.
	Additional need (high priority) for dose/efficacy/safety in bone marrow transplantation.	Agreed. List amended accordingly.
	High priority for need for dose, efficacy and safety in heart, and lung transplant > 1 year Current indication is limited to kidney transplantation > 1 yrs; need to obtain PK data in infants < 1year	Agreed. List amended accordingly. ?
Daclizumab		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	No interest in studies in other indications; not a priority, due to little experience in children	EMEA/PEG procedure for identifying paediatric needs does not include identification of priorities
Rituximab		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	High priority for need for studies in other indications Define efficacy also in post-transplant lymphoproliferative disease, severe autoimmune haemolytic anemia, refractory ITP	EMEA/PEG procedure for identifying paediatric needs does not include identification of priorities. Agreed. List amended accordingly.
Cyclophosphamide		
Line no.[1] + paragraph no.	**Comment and Rationale**	**Outcome**

[1] Where applicable

	Cyclophosphamide tablets should also be available in smaller mg samples (dividing tablets is not very exact!) - suppositories would be helpful.	Noted. Need already covered by needs identified by the PEG (Need for age appropriate formulations).
	High priority studies for new indication, as widely used also in bone marrow transplantation	Noted. Need covered in List of paediatric needs Chemotherapy I.
	It is suggested to add need: High priority to harmonize authorization and define lower age limits in children across Member States	Agreed. List amended accordingly.
Prednisolone		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Prednisolone solution has a very bitter taste, hard to swallow for children.	Noted.
Cyclosporin		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	High priority for need for studies in aplastic anemia (extension of the indication).	EMEA/PEG procedure for identifying paediatric needs does not include identification of priorities.
	There is considerable evidence on efficacy in aplastic anemia, hemophagocytic lymphohistiocyctosis of childhood, and severe autoimmune diseases. These should be considered as new indications	Partly agreed. Need for extension of the indication to hemophagocytic lymphohistiocyctosis added to the list.. Aplastic anemia already covered in the needs as identified by the PEG.
	Low priority for need for data in children < 1 year (pharmacokinetic studies) as PK data already available in different settings which simply need to be evaluated.	Agreed. List amended accordingly.
Everolimus		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Low priority for need for extension of the indication to all age groups including newborns Need to assess available PK data in children, and to evaluate	EMEA/PEG procedure for identifying paediatric needs does not include identification of priorities

	efficacy/safety data for kidney transplantation in subjects <18 years.	Noted. Already covered by needs as identified by the PEG.
ATG Thymoglobuline		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	High priority of need for studies in children all ages as widely used in bone marrow transplantation, kidney and liver transplantation, severe autoimmune disease and aplastic anemia. Need to assess available safety/efficacy data in order to grant authorization in children	Agreed. List amended accordingly. Agreed. Already covered by needs as identified by the PEG.
ATG Lymphoglobuline		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	High priority of need for studies in children all ages as widely used in bone marrow transplantation, kidney and liver transplantation, and aplastic anemia. Need to assess available safety/efficacy data in order to grant authorization in children	Agreed. List amended accordingly. Agreed. Already covered by needs as identified by the PEG.
Fluticasone cream		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Low priority for need for extension of indication < 1 year as some data on adsorption in infants/PK data already available	EMEA/PEG procedure for identifying paediatric needs does not include identification of priorities.
	Change authorized age group to: all ages (United Kingdom)	Disagree: UK SPC : Children >1 year