European Medicines Agency
Evaluation of Medicines for Human Use

London, 21 September 2006
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OVERVIEW OF COMMENTS RECEIVED ON LIST OF PAEDIATRIC NEEDS EPILEPSY

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	TEDDY (Task Force in Europe for Drug Development for the Young)	Italy
2	EFPIA (The European Federation of Pharmaceutical Industries and Associations)	Belgium
3	UCB (Biopharmaceutical company)	Belgium
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7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel: (44-20) 74 18 84 00, Fax: (44-20) 74 18 84 16
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

Table 2:Discussion of comments

GENERAL COMMENTS - OVERVIEW	
Experts agree on the need to develop drugs specifically addressed to children as treating epilepsy in children is related to specific challenges e.g. age specific toxicities of anti-epileptic drugs, the impact on learning and behavioural in study, the impact on overall health of the children. In addition, long term safety studies are required. The teratogenic effect of the newer anti-epileptic drugs is linked to this and requires ongoing study.	Agreed. No action required.
Our experts group underlines that drugs included in the list are destined to cover most of the therapeutic needs in the paediatric epilepsy field as characterized by generalised epilepsy, focal epilepsy, absence seizures, myoclonic seizures, atonic seizures, status epilepticus, West syndrome, Lennox-Gastaut syndrome and myoclonic epilepsy. However it must be emphasised that efficacy according to epilepsy syndrome as opposed to seizure type is more relevant in this population. The drugs included in the PEG list are likely to comply with the generally recognised needs for the above cited conditions. However, our experts suggest that also other substances have to be considered, because they are already in current use: for example • Stiripentol • Zonisamide • Pregabalin • Tiagabine • Pheneturide • Prednisone	▪ Stiripentol: Not agreed. Covered by unmet medical needs. ▪ Zonisamide: Agreed. Included in the list. ▪ Pregabalin: Agreed. Included in the list. ▪ Tiagabine: Agreed. Included in the list. ▪ Pheneturide: Not agreed. Covered by unmet medical needs. ▪ Prednisone: Not agreed. Covered by unmet medical needs.
The group of experts believe that differences in the age group authorised for using paediatric medicines could favour off-label and inappropriate drug utilisation. For this reason our experts suggest that a special European Procedure should be applied in order to unify, at a European level, using existing clinical evidence, paediatric use including the 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	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.

registrative or any other documentation they have at their disposal.	
In general, the expert group feels that it is priority to study the use of anti-epileptic drug in the neonatal period as only very few drugs (phenytoin and phenobarbital) are licensed as treatment of seizures in that age category.	EMEA/PEG procedure for identifying paediatric needs does not set priorities.
We suggest to include in this list also midazolam (buccal) for the study of use as emergency treatment for prolonged seizures and status epilepticus.	Already on the list.
In the majority, data are initially accumulated on anti-epileptic drugs as add-on therapy. Data are then not readily available on medication as monotherapy, as defined for licensing purposes, that is for use as first line treatment. Methodology and mechanisms for making such data available would be seen to be a priority.	Agreed, no action required.
Few data are available on the risk to the unborn child, associated with the use of newer anti-epileptic drugs in women of child bearing age. This has relevance to children as medication may be initiated, particularly in the teenage years, which will require continuation into adult hood. Pregnancy registers across Europe mean data are being accumulated as to possible teratogenetic effects of the newer drugs, but this will only enable information on malformation rate, and will require very long term data accumulation to achieve information on monotherapy on many of the newer agents.	EMEA/PEG procedure for identifying paediatric needs not extended to use of medicinal products during pregnancy.
Overall there are few RCTs available on antiepileptic drugs in children. Within the recent NICE Health Technology Appraisal on new anticonvulsant drugs for the treatment of epilepsy in children (NICE, April 2004), twenty trials were identified, only fifteen of which were published in full. In addition to the lack of paediatric trials, these RCTs are generally designed to look at efficacy over a relatively short duration, and in the majority the comparator is placebo. Of the twenty reported in the HTA, fifteen used placebo as a comparator and five used active treatments. Therefore, limited data on direct comparisons between the newer drugs are available. More comparator trials and of longer duration are required. Studies are also limited in the majority to populations of lesser clinical relevance in children – namely populations of a specific seizure type rather than epilepsy syndrome. Data accumulated often therefore has little relevance in day	Agreed. General comment, no action required.

to day clinical practice.		
The need for availability in all member states (e.g. Nitrazepam) applies to all formulations for all products (e.g. lorazepam oral liquid preparation available F not UK).		Agreed. General statement added to the list.
Valporate		
Line no.[1] + paragraph no.	**Comment and Rationale**	**Outcome**
Need	High priority for identified need for PK, safety, efficacy < 2 months Suggestion to add as a need: Open label trial of children with structural malformations (ie known aetiology)	EMEA/PEG procedure for identifying paediatric needs does not set priorities or suggests methodology to fulfil identified needs.
	Low priority for identified need for efficacy/safety in status epilepticus If to be tested would need to be done against phenytoin	EMEA/PEG procedure for identifying paediatric needs does not set priorities or suggests methodology to fulfil identified needs.
Phenobarbital		
Line no. + para no.	**Comment and Rationale**	Outcome
	No interest in defined need for long-term safety in neonates. This need is questioned as one would expect that they would discontinue or switch to alternatives when growing older.	Disagreed. Long-term safety data after neonatal use is considered of importance by the PEG
Phenytoin		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Low priority for identified need for data in long-term cognitive	EMEA/PEG procedure for identifying paediatric needs does not set priorities.

[1] Where applicable

	effects	
Lamotrigine		
Line no. + para no.	**Comment and Rationale**	Outcome
	High priority for defined need: Monotherapy in 2-12 yrs Suggestion to have multicentre data collection rather than RCT	EMEA/PEG procedure for identifying paediatric needs does not set priorities or suggest methodology to fulfil identified needs.
Authorised indication	Is 'Monotherapy in generalised and partial epilepsy' for adults or children? The current GlaxoSmithKline (GSK) Global DataSheet (GDS) also specifies tonic-clonic seizures and Lennox-Gastaut Syndrome for adults and states monotherapy in typical absence seizures only for children. Add additional indications for adults/children as appropriate	Global Data Sheets do not necessarily reflect the authorisation status in Europe. EMEA/PEG procedure for identifying paediatric needs does not include information on authorisation status in all Member States.
	Is 'Epilepsy; partial and generalised tonic-clonic seizures and seizures related to Lennox-Gastaut syndrome in combination with other antiepileptic drugs (Finland, Germany)' for adults or children? Why have only Finland and Germany been selected here? This statement is consistent with the current GSK GDS.	
	There is no mention of absence epilepsy, juvenile myoclonic epilepsy or West syndrome.	
Age group	GSK GDS allows monotherapy in children >2 years but for typical absence seizures only.	
Dose	GSK GDS allows monotherapy at 1-10 mg/kg/day, to a maximum of 200 mg/day (>2 years, but for typical absence seizures only).	
Dose	For >12 year olds, the usual maintenance dose is 100 to 200 mg as some require doses up to 500 mg	Agreed. Information added to the list.
Dose	'Different starting and maintenance doses in children < 12 years and when using with valproate (United Kingdom)' could imply monotherapy as it is currently written.	Different dosing relates to well known drug interaction between lamotrigine and valproate which requires different dosing than combination with other antiepileptics and does not imply monotherapy. Reworded to avoid misunderstanding.

Dose	There is no comment regarding the need for dose escalation in 2 to 12 year olds.	As antiepileptic treatment is in most cases individualised and dose escalation is a common recommendation, very detailed dosing recommendation is not systematically included in this document.
Dose	There is no mention of the dose regimen in children >12 years for add-on therapy.	Agreed. Information added to the list.
Dose	Include a statement that there are special requirements for using lamotrigine with valproate and carbamazepine.	Special requirement when using lamotrigine with valproate is already included in the document, as a special precaution due to specific inhibitory interaction. Other interactions similar to what is common with most antiepileptics and therefore a special mentioning is not considered necessary.
Formulations	Typographical error: 'Tablets, dispersible / chew tablets'	Agreed. List amended accordingly.
Needs	Define the 'needs' of 'Well known safety issue (skin)' as this currently is not clear.	Agreed. List reworded accordingly.
Needs	GSK GDS would currently allow 'Monotherapy in 2-12 years' but for typical absence seizures only.	Not approved in all Member States, see comment above.
Needs	Age appropriate formulations are already available in some member states eg dispersible tablets of 2 and 5 mg	Noted. Information on authorisation status in all Member States not available for PEG paediatric needs assessment procedure. Refer to EMEA/PEG procedure for identifying paediatric needs (Limits of the methodology chosen)
Needs	Include adequate treatment for patients below 2 years of age.	Agreed. Need for PK, efficacy and safety in children < 2 years added to the list.
Topiramate		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	High priority for defined need for PK/safety/efficacy < 2 yrs Trials already underway	EMEA/PEG procedure for identifying paediatric needs does not set priorities. Noted.
	Low priority for identified need for dose/efficacy/safety in SMEI Open label study, preliminary data available. Probably need for longer term follow up with neurodevelopmental data	EMEA/PEG procedure for identifying paediatric needs does not set priorities. Long term-safety already listed as need.
Levetiracetam		
Line no. + para no.	**Comment and Rationale**	**Outcome**

	Low priority for defined need for PK, safety, efficacy < 16 yrs Efficacy data now currently down to 4 years, further trials in younger age group underway. Need for data <2 years	EMEA/PEG procedure for identifying paediatric needs does not set priorities. Age group < 16 years covers children < 2 yrs.
	Levetiracetam has been approved for add-on treatment of partial onset seizures in children from the age of 4 since September 2005 and therefore we suggest that the product overview is updated accordingly. We understand that studies are ongoing to extend the age range to children from the age of 6 months.	Agreed. List amended accordingly.
Authorised age group	> 4 years (Germany, Sweden, UK, Netherlands)	
Indication	To be updated with: myoclonic seizures in patients with JME	Agreed. List amended accordingly.
Age group	To be updated: add-on therapy: > 4 years	See comments above
Dose	Starting dose of 20mg/kg/day not correct as already a therapeutic dose Proposal: Adults 1000 to 3000 mg/day Children: 20 to 60 mg/day	
Formulation	To be updated: Oral administration: tablets, oral solution Intravenous administration: concentrate for solution for infusion	Information on authorisation status in all Member States not available, as stated in EMEA/PEG procedure for identifying paediatric needs.
Needs	To be updated:	See comments above

Gabapentine

Line no. + para no.	Comment and Rationale	Outcome
Need	No interest in defined need for safety, efficacy of monotherapy in partial epilepsy < 12 yrs and of add on therapy < 3 yrs	EMEA/PEG procedure for identifying paediatric needs does not set priorities.
Authorised age group	Adjunctive therapy > 2 years (UK)	Autthorised age group according to currently available information. Information on authorisation status in all Member States not available, as stated in EMEA/PEG procedure for identifying paediatric needs.

Clobazam		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Low priority for defined need: PK, safety, efficay < 3 yrs	EMEA/PEG procedure for identifying paediatric needs does not set priorities.
Clonazepam		
Line no. + para no.	**Comment and Rationale**	Outcome
	No interest in defined need: PK, safety, efficacy < 3 months	EMEA/PEG procedure for identifying paediatric needs does not set priorities.
	No interest (priority 0) in identified need efficacy/safety of continous infusion in status epilepticus, as there is evidence other drugs, ie midazolam supercede this	EMEA/PEG procedure for identifying paediatric needs does not set priorities.
Authorised age group	> 0 years (Sweden)	No age limit (also in FI as mentioned in document) not considered alone as sufficient evidence for existence of appropriate data and therefore needs expressed
Oxcarbazepine		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Low priority for defined needs: PK, safety, efficacy < 3 yrs	EMEA/PEG procedure for identifying paediatric needs does not set priorities.
Fosphenytoin		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Low priority for defined need: PK, PD data < 5 yrs	EMEA/PEG procedure for identifying paediatric needs does not set priorities.
Midazolam		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	High priority for identified need for efficacy, safety for status epilepticus	EMEA/PEG procedure for identifying paediatric needs does not set priorities.

	Data already available on buccal midazolam. Safety data on iv use in acute situation	Already covered by 'Extension of indication for status epilepticus (efficacy, safety and dose)
Need	The buccal administration is not authorised in UK or elsewhere in EU. Therefore a formulation must be developed.	Agreed. List amended accordingly.
Felbamate		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Low priority for identified need for dose, efficacy, safety in refractory epilepsies	PEG Paediatric Needs Assessment Procedure does not set priorities.
Sultiam		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	No interest in defined need for lower age group definition	No age limit not considered alone as sufficient evidence for existence of appropriate data and therefore needs expressed, however EMEA/PEG procedure for identifying paediatric needs does not set priorities.
Paraldehyde		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Strongly disagreed that paraldehyde is devoid of any interest. Rectal paraldehyde is still useful by the rectal route (and possibly by IV infusion) for status epilepticus (probably third line) and intractable epiliepsies. There is a need for an appropriate rectal enema (the injection is licensed in UK but must be diluted in oil for rectal administration).	Agreed. Paraldehyde and identified needs added to the list.