European Medicines Agency
Evaluation of Medicines for Human Use

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ASSESSMENT OF THE PAEDIATRIC NEEDS
EPILEPSY

DISCLAIMER

The Paediatric Working Party (PEG) is working to identify the needs in the different therapeutic areas where there should be research and development of medicinal products for children, either old (i.e. off patent) or new ones (including those under development). Products on the list are not in any order of priority.

The lists should not be viewed as a prescription tool nor as recommendations for treatment. Accuracy of data including in particular authorised doses cannot be guaranteed.

Information on existing marketing authorisations is very limited and therefore information under "authorised" includes the indication in broad term (only related to neurology), the lower age group authorised in at least one Member State, the authorised dose(s) (if authorised for use in patients less than 18 years of age) and formulation(s) in at least in one Member State.

Please refer to the EMEA/PEG procedure for identifying the paediatric needs for further information.

Comments from third parties are expected especially to complete and or update the list as necessary.

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GENERAL NEED:

Due to the fact that long-term safety data is largely not available for the following medicinal products, the Paediatric Working Party (PEG) defined as an overall need the production of safety data in long term use (including effects on cognition). In addition, the Paediatric Working Party (PEG) identified the need for studies of medicinal products for refractory epilepsies.

If not stated separately, the need for availability in all Member States of the Community applies to all medicinal products included in this list.

ANTICONVULSANTS	
VALPROATE	
Authorised indication	Generalised Epilepsy, partial and focal seizures, absence, myoclonic and atonic seizures (*Finland)* Prevention of febrile seizures (*France*)
Authorised age group	All age groups (*Finland*)
Authorised dose	Children: 15-30 mg/kg/day Adolescents 30 mg /kg /day
Authorised formulation	I.v., tablets, liquid formulation, retard formulations slow release microparticulate formulation (*France*), rectal suppositories
Needs	PK and safety of higher dose (used off-label), Age appropriate formulation for high dose treatment Long-term safety data PK, safety and efficacy in children < 2 months Efficacy and safety in status epilepticus
PHENOBARBITAL	
Authorised indication	Monotherapy or concomitantly with other anticonvulsants treatment of generalised epilepsy: clonic seizures, tonic seizures, tonic-clonic seizures; treatment of partial epilepsy: partial seizures, whether or not secondarily generalised
Authorised age group	All age groups
Authorised dose	Loading dose: 20 mg/kg Long-term: Children < 20 kg: 5 mg/kg/day 20-30 kg: 3-4 mg/kg/day, > 30 kg: 2-3 mg/kg/day
Authorised formulation	I.v., tablets, Elixir containing alcohol (*United Kingdom*)
Needs	Long-term safety data after neonatal use Alcohol-free age appropriate liquid and i.v. formulation
CLOBAZAM	
Authorised indication	Epilepsy; concomitant add-on therapy only (*Finland*)
Authorised age group	> 3 years, from 6 months to 3 years only in exceptional cases when absolutely necessary (*Austria*)
Authorised dose	Max 30 mg/day; max. dose 80 mg/kg in children >15 years, 1 mg/kg in children 3-15 years (*Finland*)
Authorised formulation	Tablet (*United Kingdom*) 5+10 mg capsules (*France*)
Needs	Data on PK, efficacy and safety < 3 years Long-term efficacy (incl. tolerance) data in all age groups Cognitive effects in long term use Age appropriate formulation
CLONAZEPAM	
Authorised indication	Emergency treatment of seizures and long-term add-on treatment in drug-resistant cases

Authorised age group	> 3 months (no age limit in *Finland*)
Authorised dose	Very slow injection Infants: 0.125– 0.25 mg, Children: 0.5 mg (below 30 kg starting dose 0.01-0.03 mg/kg/day, maintenance 0.05-0.1 mg/kg/day; above 30 kg starting dose 1-2 mg/day, maintenance 1.5-3 mg/day (*Finland*) Adolescents: 1 mg Maximum 13 mg i.v. – therapeutic max. dose 20 mg/day (*Finland*)
Authorised formulation	I.v., 2 mg and 0,5 mg tablets (*Finland*), oral solution 2.5 mg/ml (*France*)
Needs	PK, safety and efficacy in infants < 3 months PK, efficacy and safety of continuous i.v. infusion in Status epilepticus Cognitive effects in long term use Appropriate formulation in infants < 3 months
DIAZEPAM	
Authorised indication	Emergency treatment of seizures Febrile seizures
Authorised age group	All age groups
Authorised dose	0.5 mg/kg Maximum 10 mg i.v.
Authorised formulation	I.v., oral solutions, rectal solutions, tablets
Needs	Age appropriate formulations for acute ambulatory treatment of seizures in children
LORAZEPAM	
Authorised indication	Status epilepticus
Authorised age group	all age groups (*United Kingdom*)
Authorised dose	100 micrograms/kg, max 4 mg (1month-12 years)
Authorised formulation	Injection (*United Kingdom*), oral formulation (*France*), 0.5, 1.0, 2.0 and 2.5 mg tablets (*Germany*)
Needs	Age appropriate buccal and rectal formulations
MIDAZOLAM	
Authorised indication	Sedation in ICU and anaesthesia
Authorised age group	All age groups
Authorised dose	I.v.: 150-200 micrograms/kg as a single dose, followed by continuous infusion 1 microgram/kg/minute Buccal administration: 300 micrograms/kg
Authorised formulation	I.v., buccal liquid (*United Kingdom*)
Needs	Safety reassessment (preclinical, PK, PD, safety) PK data for buccal liquid Extension of indication for status epilepticus, (efficacy, safety and dose)
NITRAZEPAM	
Authorised indication	Infantile spasms (as in West Syndrome), Lennox-Gastaut syndrome and myoclonic epilepsy (*Finland*)
Authorised age group	All ages (*Finland, Austria*)
Authorised dose	< 1 year 5-10 mg/day Toddlers and school-age 15 mg/day
Authorised formulation	Oral liquid (*United Kingdom*) tablet 5 mg/10 mg (*Finland*)
Needs	Availability in all Member States
CARBAMAZEPINE	

Authorised indication	First line in partial epilepsy
Authorised age group	All ages (*Finland*)
Authorised dose	10-20 mg/kg/day; < 1 year: 100-200 mg/day (*Finland*) 1-5 year: 200-400 mg/day (*Finland*) 5-10 year: 400-600 mg/day (*Finland*) 10-15 year: 600-1000 mg/day (*Finland*)
Authorised formulation	I.v., oral suspension, tablets, chew tabs, sustained release tabs, suppositories (*United Kingdom*)
Needs	Age appropriate slow release formulations
OXCARBAZEPINE	
Authorised indication	Partial epilepsy
Authorised age group	> 3 years (*Finland*)
Authorised dose	8–60 mg/kg/day
Authorised formulation	Oral suspension, tablets
Needs	Data on PK, efficacy and safety in children < 3 years Long-term safety Age appropriate slow release formulation
ETHOSUXIMIDE	
Authorised indication	Generalised absence seizures in patients with also generalised tonic-clonic seizures, alone and in combination with other anticonvulsants
Authorised age group	All ages (*Finland*)
Authorised dose	Children 20 mg/kg/day Starting dose in children < 6 years 250 mg/day, in children > 6 years and adults 500 mg/day
Authorised formulation	Oral solutions, tablets, capsules, liquid formulation (*Austria, Germany, Finland*)
Needs	Bioavailability and bioequivalence issues for different formulations, resulting in interchangeability problems
PHENYTOIN	
Authorised indication	Epilepsy; focal seizures with or without secondary generalisation (*Finland*)
Authorised age group	p.o all ages
Authorised dose	p.o.: 4-8 mg/kg/day i.v.: Loading dose Newborn: 8-12 mg/kg 15-18 mg/kg (*United Kingdom*) 15 mg FE/kg (*Finland*) Children: 10-15 mg/kg 15 mg FE/kg (*Finland*) Maintenance: Newborn: 3-5 mg/kg 4-5 mg FE/kg/day (*Finland*) Children: 7-10 mg/kg 4-5 mg FE/kg/day (*Finland*)
Authorised formulation	I.v., tablets, capsules, chew tabs, suspension (*United Kingdom, Germany, Switzerland, Spain, France, Belgium)*
Needs	Need for high concentration oral suspension required e.g. 90 mg/5ml Need for data on cognitive effects in long-term use
FOSPHENYTOIN	
Authorised indication	Epilepsy; focal seizures with or without secondary generalisation Status epilepticus
Authorised age group	I.v. > 5 years
Authorised dose	Fosphenytoin i.v.

	Loading dose: Newborn: 8-12 mg/kg 15-18 mg/kg (*United Kingdom*) 15 mg FE/kg Children: 10-15 mg/kg 15 mg FE/kg (*Finland*) Maintenance dose: Newborn: 3-5 mg/kg 4-5 mg FE/kg/day (*Finland*) Children: 7-10 mg/kg 4-5 mg FE/kg/day (*Finland*
Authorised formulation	I.v.
Needs	PK/PD data in children < 5 years (but should generally be used only under drug monitoring)
SULTIAM	
Authorised indication	Benign partial epilepsy (Rolando), as a second line drug (*Germany*)
Authorised age group	All ages (*Austria*)
Authorised dose	5-10 mg/kg/day
Authorised formulation	Tablets (50 and 200 mg)
Needs	Define lower age limit based on existing data on efficacy and safety and investigate where needed, including in newborns
VIGABATRIN	
Authorised indication	Monotherapy in West Syndrome, Combination therapy in drug resistant focal epilepsy and secondary generalised epilepsy
Authorised age group	All ages
Authorised dose	Starting dose: 40 (50) mg/kg/d up to 100 or 150 mg/kg/day for spasms Maintenance dose: 10-15 kg: 0,5-1 g/day 15-30 kg: 1-1,5 g/day 30-50 kg: 1,5-3 g/day > 50 kg: 2-3 g/day
Authorised formulation	Tablets, oral granules/powder sachet (*United Kingdom, Germany)*
Needs	Age appropriate formulations (for small doses) Note; well known safety issue (vision) currently under active surveillance
LAMOTRIGINE	
Authorised indication	Monotherapy in generalised and partial epilepsy Epilepsy; partial and generalised tonic-clonic seizures and seizures related to Lennox-Gastaut syndrome in combination with other antiepileptic drugs (*Finland, Germany*)
Authorised age group	Monotherapy > 12 years Combination (add-on) > 2 years
Authorised dose	> 12 years monotherapy; 100-200 mg /day Different starting and maintenance doses in children < 12 years when used with valproate (*United Kingdom*) > 12 years: maintenance dose in combination (add-on) and monotherapy 100-200 mg/day.
Authorised formulation	Tablets, dispersible /chewable tablets (*United Kingdom)*
Needs	Further characterisation of the well known safety issue (skin reactions) Monotherapy in 2-12 years extension of indication Age appropriate formulation available in all MS's Need for PK, efficacy and safety in children < 2 years.
TOPIRAMATE	
Authorised indication	Generalised and partial epilepsy, monotherapy, combination therapy
Authorised age group	> 2 years

Authorised dose	Monotherapy: Starting dose 0.5-1 mg/kg/day (*United Kingdom*) increase in 0,5-1 mg/kg steps, target dose: 3-6mg/kg/day Combination therapy: starting dose: 0,5-1mg/kg/day increase in 1mg/kg steps target dose: 5-9 mg/kg/day
Authorised formulation	Tablets, capsules (*United Kingdom*)
Needs	PK, efficacy and safety data in children < 2 years Extension of indication in SMEI (severe myoclonic epilepsy in infancy) (dose, safety and efficacy) Long-term safety, including cognitive effects Age appropriate formulation
GABAPENTINE	
Authorised indication	Partial epilepsy, Complex focal epilepsy (only add-on *Finland*)
Authorised age group	> 12 years Add on therapy > 3 years (*France*, *Germany*)
Authorised dose	> 12 years: Starting dose: 900 mg/day Maintenance dose: 2400 - 3600 mg/day 3-12 years: Starting dose 10 mg/kg/day Maintenance dose: 30 mg/kg/day
Authorised formulation	Capsules, tablets
Needs	Efficacy and safety of monotherapy in partial epilepsy < 12 years Efficacy and safety of add on therapy < 3 years Age appropriate formulation.
LEVETIRACETAM	
Authorised indication	Epilepsy; partial seizures with or without secondary generalisation, add-on therapy, myoclonic seizures in children > 12 years with Juvenile Myoclonic Epilepsy
Authorised age group	> 4 years
Authorised dose	Starting dose 20 mg/kg/day, maintenance dose 40-60 mg/kg/day
Authorised formulation	Tablets, oral solution
Needs	Data on PK, efficacy and safety in children < 4 years in partial and generalized epilepsy
FELBAMATE	
Authorised indication	Combination therapy in refractory Lennox-Gastaut syndrome
Authorised age group	> 4 years
Authorised dose	< 14 years: 600-1200 mg, maximum dose: 3600 mg/day 4-14 years: 7.5-15 mg/kg/day maximum dose: 45 mg/kg/day or 3600 mg/day
Authorised formulation	Capsules, tablets, oral solution: 600mg/5ml (*Germany*)
Needs	Long term safety data including effects on cognitive function Extension of indication in refractory epilepsies, (Dose, efficacy and safety)
ACTH	
Authorised indication	Infantile spasms (West syndrome, Lennox-Gastaut syndrome)
Authorised age group	> 1 month
Authorised dose	0.25 mg/day

	maintenance dose 0.25 mg/every 2-8 days
Authorised formulation	I.m.
Needs	Availability in all member states Need for age appropriate depot formulation
PARALDEHYDE	
Authorised indication	Status epilepticus
Authorised age group	Not authorised in children
Authorised dose	-
Authorised formulation	-
Needs	
ZONEGRAN	
Authorised indication	Adjunctive therapy in adult seizures with or without secondary generalisation
Authorised age group	Not authorised in children
Authorised dose	-
Authorised formulation	-
Needs	
PREGABALIN	
Authorised indication	Adjunctive therapy in adult seizures with or without secondary generalisation
Authorised age group	Not authorised in children
Authorised dose	-
Authorised formulation	-
Needs	
TIAGABINE	
Authorised indication	Adjunctive treatment of partial seizures with or without secondary generalisation not satisfactorily controlled by other antiepileptics
Authorised age group	> 12 years
Authorised dose	Initially 5mg twice daily, increased at weekly intervals
Authorised formulation	Tablets
Needs	

The PEG considers that the following products are devoid of any therapeutic interest in paediatrics

PRIMIDONE

UNMET MEDICAL NEEDS	
REFRACTORY/INTRACTABLE EPILEPSY	
Proposed indications:	Anticonvulsive treatment
Needs	Effective monotherapy or combinations of existing or new antiepileptics