European Medicines Agency
Evaluation of Medicines for Human Use

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OVERVIEW OF COMMENTS RECEIVED ON LIST OF PAEDIATRIC NEEDS – CARDIOVASCULAR PRODUCTS

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

	Name of Organisation or individual	Country
1	Merck sharp & Dohme	Belgium
2	Joe Degiovanni, Maltese Cardiologist	Malta
3	EFPIA (The European Federation of Pharmaceutical Industries and Associations)	Belgium
4	TEDDY (Task-force in Europe for Drug Development for the Young)	Italy
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GENERAL COMMENTS - OVERVIEW	
Renovascular disorders should be considered in a next assessment of paediatric needs. Concerns are expressed because many drugs in the same clinical category (see hypertension) are listed at the same level of the need. 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 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.	Renovascular disorders partly covered by List of paediatric needs Nephrology (under preparation) EMEA/PEG procedure for identifying paediatric needs does not include identification or setting of priorities.
We suggest the inclusion of the following new products in the list: • colesevelam • dofetilide • irbesartan/hydrochlorothiazide • ivabradine • telmisartan • telmisartan/hydrochlorothiazide	Colesevelam: Included in the list Dofetilide: not authorised, not included in the list Irbesartan/hydrochlorothiazide: not included, the PEG does not agree that there is a need for fixed combinations in the paediatric population Ivabradine: Included in the list Ivabradine: No data, not included in the list Telmisartan: Included in the list Telmisartan/hydrochlorothiazide: not included, the PEG does not agree that there is a need for fixed combinations in the paediatric population.

MILRINONE		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Under indications: to include low cardiac output especially after heart surgery	Agreed. Included in the list.

ENOXIMONE		
Line no. + para no.	**Comment and Rationale**	**Outcome**

	Increasingly used orally for extreme heart failure usually as a bridge to transplant. i.v. preparation given orally. Not licensed	Noted.
	Authorised formulation: 100 mg/ml, **150 mg/ml** solution for injection	Noted. List amended accordingly.
SILDENAFIL		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Formulations in Malta 25, 50 and 100 mg	Noted. List amended accordingly.
DOBUTAMINE		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Authorised age group: children (Spain, Germany)	Noted. List amended accordingly.
ARGININE-VASOPRESSINE		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Authorised age group: > 0 years (Sweden)	Noted. Please refer to the EMEA/PEG procedure for identifying paediatric needs / Limits of the methodology.
DIHYDRALAZINE		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Authorised age group: > 0 years (Spain)	Noted. Please refer to the EMEA/PEG procedure for identifying paediatric needs / Limits of the methodology.
NITROPRUSSIDE NATRIUM		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Authorised age group: Children (Spain)	Noted. Please refer to the EMEA/PEG procedure for identifying paediatric needs / Limits of the methodology.
EPINEPHRINE		
Line no. +	**Comment and Rationale**	**Outcome**

para no.		
	Note about incompatibility with bicarbonate as it is a common mistake during resuscitation	Noted. List of paediatric needs do not serve as a prescription tool nor as a recommendation for treatment (see disclaimer).
NOREPINEPHRINE		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Note about incompatibility with bicarbonate as it is a common mistake during resuscitation	Noted. List of paediatric needs do not serve as a prescription tool nor as a recommendation for treatment (see disclaimer).
INDOMETHACIN (IV)		
Line no.[1] + paragraph no.	**Comment and Rationale**	**Outcome**
	Marketing authorizations for indomethacin i.v. formulation and the indication for PDA exist in six EU countries (Belgium, Ireland, Luxembourg, Netherlands, Spain and UK). On 26/08/2005 the European Commission approved PEDEA (ibuprofen) solution for injection assessed via the Centralized Procedure for the orphan indication patent ductus arteriosus (PDA) in preterm newborn infants less than 34 weeks of gestational age. Since PEDEA is in principle available in all EU MS for the identified paediatric need indication, it is believed that this information should be included in the table. It should be reflected that the paediatric needs for indomethacin i.v. are covered by PEDEA and therefore, have a very low priority.	Noted. The PEG considers that there is still a need for the availability in all Member States. EMEA/PEG procedure for identifying paediatric needs does not include identification or setting of priorities.
	Slow iv over 30 mins	Noted.
CAPTOPRIL		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Authorised age group: > 0 years (Spain)	Agreed. Please refer to the EMEA/PEG procedure for identifying paediatric needs / Limits of the methodology.
ENALAPRIL		

[1] Where applicable

Line no. + para no.	Comment and Rationale	Outcome
	1) Authorized formulations also include tablets of 10 mg, 20 mg and 40 mg. 2) Hypertension -- Paediatric Population: the EU-SPC has been amended with dosing information as follows during the Article 30 referral procedure in December 2003[2]: "There is limited clinical trial experience of the use of RENITEC in hypertensive paediatric patients (see 4.4 Special warnings and special precautions for use, 5.1 Pharmacodynamic properties and 5.2 Pharmacokinetic properties). For patients who can swallow tablets, the dose should be individualized according to patient profile and blood pressure response. The recommended initial dose is 2.5 mg in patients 20 to <50 kg and 5 mg in patients ≥50 kg. RENITEC is given once daily. The dosage should be adjusted according to the needs of the patient to a maximum of 20 mg daily in patients 20 to <50 kg and 40 mg in patients ≥50 kg. (See 4.4 Special warnings and special precautions for use.). RENITEC is not recommended in neonates and in paediatric patients with glomerular filtration rate 30 ml/min/1.73 m^2, as no data are available." 3) Hypertension -- Extemporaneous formulation An extemporaneous formulation can be prepared with the use of the 20 mg tablet to form a suspension for paediatric administration. The necessary syrup and stabilizator can be obtained from a distributor in Germany. Method of preparation of the suspension and 4-weeks stability documentation is available for submission. Availability of the suspension extends the administration to patients as young as 2 months old.	Agreed. List amended accordingly. Noted.
	Authorised age group: > 28 days (Spain)	Noted. Please refer to the EMEA/PEG procedure for identifying paediatric needs / Limits of the methodology.
NIFEDIPINE		

[2] http://www.emea.eu.int/pdfs/human/referral/renitec/317503en.pdf

Line no. + para no.	Comment and Rationale	Outcome
	Come in Capsules with liquid inside too	Noted. Please refer to the EMEA/PEG procedure for identifying paediatric needs / Limits of the methodology.
	Authorised age group: children (Spain)	Noted. Please refer to the EMEA/PEG procedure for identifying paediatric needs / Limits of the methodology.
VERAPAMIL		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Authorised age group: > 0 years (Sweden)	Noted. Please refer to the EMEA/PEG procedure for identifying paediatric needs / Limits of the methodology.
CLONIDINE		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Also come in tablets of 100/300ug Authorised age group: Children (Spain)	Noted. Please refer to the EMEA/PEG procedure for identifying paediatric needs / Limits of the methodology.
LABETALOL		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Also in 50 mg tabs. The solution in Malta is 5mg/ml Authorised age group: children (Spain)	Noted. Please refer to the EMEA/PEG procedure for identifying paediatric needs / Limits of the methodology.
PRAZOSIN		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Authorised age group: children (Spain)	Noted. Please refer to the EMEA/PEG procedure for identifying paediatric needs / Limits of the methodology.
PROPRANOLOL		
Line no. +	**Comment and Rationale**	**Outcome**

para no.		
	Authorised age group: > 0 years (Spain)	Noted. Please refer to the EMEA/PEG procedure for identifying paediatric needs / Limits of the methodology.
SOTALOL		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Authorised age group: children (Spain)	Noted. Please refer to the EMEA/PEG procedure for identifying paediatric needs / Limits of the methodology.
CARVEDILOL		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Indication here should be heart failure only	Disagreed. Indication for hypertension and angina authorised in Germany.
ESMOLOL		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Authorised age group: > 2 years (Spain)	Noted. Please refer to the EMEA/PEG procedure for identifying paediatric needs / Limits of the methodology.
AMIODARONE		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Authorised > 3 years (United Kingdom)	Noted. Please refer to the EMEA/PEG procedure for identifying paediatric needs / Limits of the methodology.
FLECAINIDE		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Authorised in children > 12 years in Malta	Noted. Please refer to the EMEA/PEG procedure for identifying paediatric needs / Limits of the methodology.

ADENOSINE TP		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Authorised age group: > 0 years (Sweden)	Noted. Please refer to the EMEA/PEG procedure for identifying paediatric needs / Limits of the methodology.
PROPAFENONE		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	In Malta 6 - 12 mg/Kg/Day in divided doses is used Authorised age group: > 8 years (United Kingdom)	Noted. List amended accordingly.
LIDOCAIN		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Authorised age group: children (Spain)	Noted. Please refer to the EMEA/PEG procedure for identifying paediatric needs / Limits of the methodology.
HYDROCHLOROTHIAZIDE/CHLOROTHIAZIDE		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	The current clinical practice indicates preference for ACE Inhibitors and CCB in the treatment of hypertension in paediatric patients. Hydrochlorothiazide has less efficacy as monotherapy in children; however it is useful in combination. Hence, it is believed that the paediatric need identified for this product has a low priority Authorised age group: > 0 years (Spain)	Noted. EMEA/PEG procedure for identifying paediatric needs does not include identification or setting of priorities. Noted. Please refer to the EMEA/PEG procedure for identifying paediatric needs / Limits of the methodology.
IRBESARTAN		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Authorised indication: add: **renal disease**	Noted. List amended accordingly.

	Authorised formulation: add: **150 mg, 300 mg** tablet	
ATORVASTATIN		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Authorised age group: > 4 years (Sweden, Spain)	Noted. Please refer to the EMEA/PEG procedure for identifying paediatric needs / Limits of the methodology.
PRAVASTATIN		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Also in 10mg tablets in Malta	Noted. Please refer to the EMEA/PEG procedure for identifying paediatric needs / Limits of the methodology.
LOVASTATIN		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Authorized formulations include 10 mg, 20 mg and 40 mg tablets. Authorized doses include 10-80 mg Lovastatin has been studied in adolescent paediatric patients of 10-17 years of age, with heterozygous familial hypercholesterolaemia. The respective clinical documentation is available for submission in the EU countries via the Paediatric EU work sharing project. In this age group the tablet formulation can be used. Long-term efficacy and safety (EXCEL) and clinical outcome studies (AFCAPS; primary prevention of acute major coronary events) have been conducted in adults. A clinical outcome study specifically for children is probably not feasible, nor warranted.	Noted. List amended accordingly. Noted.
	Authorised age group: > 10 years (Spain)	Noted. Please refer to the EMEA/PEG procedure for identifying paediatric needs / Limits of the methodology.
SIMVASTATIN		
Line no. + para no.	**Comment and Rationale**	**Outcome**

	Authorized formulations include 5 mg, 10 mg, 20 mg, 40 mg and 80 mg tablets.Authorized doses include 5-80 mg Simvastatin has been assessed in adolescent paediatric patients of 10-17 years of age, with heterozygous familial hypercholesterolaemia. The respective clinical documentation is available for submission in the EU countries via the Paediatric EU work sharing project. In this age group the tablet formulation can be used.	Noted. List amended accordingly Noted.
	10/20/40/80 mg tablets in Malta	Noted. List amended accordingly.
	Authorised age group: > 10 years (Spain)	Noted. Please refer to the EMEA/PEG procedure for identifying paediatric needs / Limits of the methodology.
CLOPIDOGREL		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Antiplatelet agent. Also oral preparation in Malta	Noted. List amended accordingly.
	Authorised formulation: add: **75 mg film-coated tablet** Delete "intravenous solution"	Noted. List amended accordingly. Agreed. Intravenous formulation not available in France, Germany or the United Kingdom.
DALTEPARINE		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Authorised age group: > 2 years (Italy)	Noted. Please refer to the EMEA/PEG procedure for identifying paediatric needs / Limits of the methodology.
	Also in 25000/ml in Malta	Noted. List amended accordingly.
ACETYLSALICYLIC ACID (ASPIRINE)		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Anteplatelet agent. Indications to include maintaining shunt patency and for post-implantation of cardiac devices for ASD and VSD	Noted. Already covered in the indication.

	Authorised age group: no age limit specified (Spain)	Noted. Please refer to the EMEA/PEG procedure for identifying paediatric needs / Limits of the methodology.
DIPYRIDAMOLE		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	25/50/100 mg tabs in Malta	Noted. List amended accordingly.
LOW MOLECULAR WEIGHT HEPARINS		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Authorised formulation: add: **150 mg/ml** solution for injection	Noted. List amended accordingly.
PROTAMINE		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	To reverse heparin overdose or side effects. Not licensed.	Noted. Transferred to list of paediatric needs anaesthesiology.
LOSARTAN		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Suggestion to include Losartan in the list: COZAAR (losartan potassium) is available in most of the EU Member States. Approved indications: hypertension and heart failure Approved dosage form: tablet Approved strengths: 12.5 mg, 25 mg, 50 mg and 100 mg Approved age group: adults; children age 6 and above (UK only) For the paediatric investigation of losartan two clinical trials have been conducted in paediatric patients: an open-label study to investigate the pharmacokinetics of losartan in hypertensive children and infants and a double-blind, randomized dose-response study of losartan in children with hypertension. The respective clinical documentation has been evaluated by the	Noted. The assessment of the paediatric data via the Paediatric Eu work sharing awaited.

	MHRA and has been prepared for assessment via the Paediatric EU work sharing project. In the older age group the tablet formulation can be administered. An extemporaneous formulation can be prepared with the use of the 50 mg tablet to form a suspension for paediatric administration. The necessary syrup can be obtained from a distributor in Germany. Method of preparation of the suspension and 4-weeks stability documentation is available for submission. Availability of the suspension extends the administration to patients as young as 6 years old.	
LISINOPRIL		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Is the commonest long acting ACE inhibitor used. Not licensed but used for hypertension and heart failure	Noted. At this stage, it is considered that the ACE inhibitors already mentioned in the list cover the need
AMILORIDE		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Commonest adjunct to furosemide as potassium sparing diuretic; more commonly used than spironolactone. Not licenced for children.	Noted. Diuretics will be covered through list of paediatric needs Nephrology (under preparation).
NITRATES		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	For hypertension, angina (eg Kawasaki or cardiomyopathy). Not licensed.	Noted.
IBUPROFEN		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Less toxic than indomethacin with respect to renal dysfunction. Licenced for premature babies to close PDA in those under 34 weeks	See comment on indomethacin.

	gestational age.	
PROSTAGLANDIN		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	We are surprised this is not on the list having transformed the practice and results in congenital heart disease. Prostin E1 or Prostin E2 can be given i.v. Prostin E2 can be given via NG tube. Tablets or iv solution.	Noted. Prostaglandin E1 already authorised in congenital heart disease.
DIGOXIN		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Still used both for heart failure and arrhythmias and is licensed for both these in children -- for a change as 70% of the drugs we use are not licenced for kids	Noted.
UROKINASE		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Authorised age group: children (Spain)	Noted. Please refer to the EMEA/PEG procedure for identifying paediatric needs / Limits of the methodology.