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Human Medicines Development and Evaluation

Revised provisional priority list for studies into off-patent paediatric medicinal products

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Agreed by PDCO	
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Comments should be provided using this template. The completed comments form should be sent to paediatrics@ema.europa.eu

This provisional priority list of off-patent medicines is intended to be the basis for potential future funding within the Horizon 2020 Programme of the European Commission. As preparations for Horizon 2020 still are under way, no further information can be provided concerning the availability, timing and organisational aspects of any possible future calls involving off-patent paediatric medicinal products.

Submitting a paediatric investigation plan (PIP) before applying for funding is encouraged, to receive the Paediatric Committee's (PDCO) opinion on the development plan in advance. Further information can be found below in the section 'Notes'.

Objective of the list

The aim of Regulation (EC) No1901/2006 of the European Parliament and the Council on Medicinal Products for Paediatric Use is to increase availability of medicines authorised for children as well as to

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increase the information available on the use of medicinal products in the paediatric population. The Regulation includes provisions for funding studies into off-patent medicinal products. In the case of the availability of funding, , it should cover the development of off-patent medicinal products with a view to the submission of a Paediatric Use Marketing Authorisation (PUMA; Art. 30, Regulation [EC] No 1901/2006).

Agreement on the specific content of a PUMA application will eventually be through a Paediatric Investigation Plan (PIP).

Notes

- The following are always considered to be of high priority:
  - Development of age-appropriate formulations and strengths (even if not explicitly stated);
  - Data in neonates for all conditions (except oncology);
  - Data in infants for oncological conditions and for refractory paediatric epilepsy syndromes.
- Prioritised needs, as listed in the column 'Priority', do not necessarily cover all needs for the treatment of the paediatric population, nor will they automatically cover the regulatory requirements for a Paediatric Investigation Plan (PIP). In other words, whereas not all conditions mentioned for an active substance have to be investigated, all paediatric age groups must be covered either by a PIP or a waiver.
- Applicants are encouraged **to submit a PIP before applying for funding**, in order to receive the Paediatric Committee's (PDCO) opinion on the development plan. Further information regarding the PIP can be obtained:
  - as a first step from the website of the European Medicines Agency (EMA)
  - through a pre-submission teleconference with the EMA

  It should be noted that the PIP is a 120-day procedure with a clock-stop phase, during which the applicant can amend the PIP according to the requests and proposals of the PDCO. Therefore an early application is advisable.

Disclaimer

The list includes only products considered to be off-patent, i.e. not covered by a basic patent or a supplementary protection certificate. Information on the authorisation status as well as on available paediatric formulations of medicinal products is limited and not available for all European Member States. Information on the off-patent and authorisation status is not guaranteed by the EMA. Users of this list should check the patent status and the authorisation status of the medicinal products of interest.

The methodology used to establish the list was based as much as possible on evidence-based medicine (see p.12). It is however acknowledged that identification of priorities for research into medicinal products for paediatric use is partly based on subjective criteria and that identified priorities may change over time. This may also be the case should further information of which the Paediatric Committee is not aware become available (e.g. on pharmacokinetics, safety and efficacy, submission of PIPs for prioritised products, etc.). Projects for an active substance already funded, such as for the development of age-appropriate formulations for a particular product, should not be re-submitted. Please check the website of the European Commission for already funded projects.

The products are listed according to their therapeutic field and condition(s) in alphabetical order.

Therapeutic field	Product	Condition(s)	Priority
Cardiology	(refer also to 'nephrology' for hypertension)		
	amiodarone	Supraventricular and ventricular arrhythmia	Data on pharmacokinetics (PK), efficacy and long-term safety.
	propranolol	Supraventricular tachycardia	Data on PK, efficacy and safety.
Child & adolescent psychiatry			
	fluoxetine	(1) Major depressive disorder (MDD) with psychotic symptoms (2) General anxiety disorder (GAD), obsessive compulsive disorder (OCD)	(1) Data on short and long term-safety. (2)Data on short and long term-safety and efficacy.
Dermatology	(refer also to 'immunology' and 'rheumatology')		
Endocrinology			
	androstanolone gel	(1) Micropenis (2) severe hypospadias	(1,2) Data on PK, efficacy and safety.
	cholestyramine	Hypercholesterolaemia	Data on efficacy and safety in children from 6 years. Palatable age-appropriate formulation.
	glibenclamide	Diabetes mellitus type II	Data on PK, efficacy and safety in children from 10 years.
Gastroenterology	(refer also to 'immunology')		
	bisacodyl	Constipation	Data on long-term efficacy, safety, all age groups; age-appropriate formulation.
	omeprazole	Ulcer prophylaxis in intensive care unit (ICU) patients	Data on PK, safety, efficacy for intravenous and gastric (i.e. via feeding tube) use.
	mesalazine	Ulcerative colitis	Data on efficacy and safety compared to sulphasalazin

Therapeutic field	Product	Condition(s)	Priority
Haematology / Haemostaseology			
	alteplase	Deep vein thrombosis, acute arterial thrombosis, catheter-related arterial thrombosis	Data on PK, efficacy and safety; age-appropriate formulation. All age groups including neonates.
	unfractionated heparin	Anticoagulation	Data on PK, efficacy and safety.
Immunology	(refer also to 'oncology', 'gastroenterology' and 'rheumatology')		
	azathioprine	(1) Crohn's disease (2) Ulcerative Colitis (3) Severe atopic dermatitis (4) Systemic lupus erythematosus, systemic vasculitides	(1) Data on efficacy and safety in combination with biologicals such as anti tumour necrosis factor (TNF); age-appropriate formulation. (2) Data on efficacy and safety, possible reduction of relapse, steroid use and delay/avoiding surgery; age-appropriate formulation. (3) Data on efficacy and safety; age-appropriate formulation. (4) Data on PK, efficacy and safety; age-appropriate formulation.
	ciclosporin	(1) Nephrotic syndrome (2) Juvenile idiopathic arthritis (JIA)-related uveitis, macrophage activation syndrome (MAS) / haemophagocytic lymphohistiocytosis (HLH), juvenile dermatomyositis	(1) Data on PK, long-term efficacy and safety. (2) Data on PK, long-term efficacy and safety.

Therapeutic field	Product	Condition(s)	Priority
	methotrexate	(1) Crohn's disease (2) Ulcerative Colitis (3) Juvenile dermatomyositis, childhood scleroderma, Juvenile idiopathic arthritis -related uveitis (4) Systemic lupus erythematosus	(1) Data on efficacy and safety [including combination with biologicals such as anti-TNF]. (2) Data on efficacy and safety, possible reduction of relapse, steroid use and delay/avoiding surgery. (3) Data on PK, efficacy and safety. (4) Data on PK, efficacy and safety.
	mycophenolate mofetil	(1) Short and long term immunosuppression for prevention of graft rejection and graft versus host disease after allogenic haematopoetic stem cell transplantation (HSCT) (2) Renal, heart and liver transplantation (3) Chronic autoimmune hepatitis (4) Systemic lupus erythematosus nephritis, nephrotic syndromes (5) Systemic vasculitides, juvenile dermatomyositis, scleroderma, JIA-related uveitis	(1) Data on PK, efficacy and safety. (2) Data on PK, efficacy and safety (renal transplantation: 0-2 years, heart and liver transplantation: all age groups) (3) Data on PK, efficacy and safety. (4) Data on PK, efficacy and safety. (5) Data on PK, efficacy and safety.

Therapeutic field	Product	Condition(s)	Priority
Infections	(refer also to 'pneumology')		
	amphotericin B	Mycotic infections	Data on efficacy and safety in immuno-compromised patients in all age groups, including neonates and preterm infants.
	clindamycin	Osteomyelitis; infections caused by Methicillin resistant *Staphylococcus aureus* and Methicillin resistant *Staphylococcus epidermidis*	Data on PK (unless available) in all age groups; relevant tissue and fluid levels; short- and long-term efficacy and safety.
	ganciclovir	Cytomegalovirus infection	Data on PK, efficacy and safety in immuno-compromised patients in all age groups, neonates, and preterm infants. Age-appropriate oral formulation.
	isoniazid (H) rifampicin (R) ethambutol (E) pyrazinamide (Z)	Tuberculosis	Age-appropriate fixed dose combinations: HRZE, HRZ, HR PK and dose recommendations.
	itraconazole	Invasive mycotic infections, aspergillosis, chronic granulomatous disease, febrile neutropenia, cystic fibrosis.	Data on PK, efficacy and safety.
Intensive care / anaesthesiology	(refer also to other fields such as 'cardiology', 'haematology', 'infections', 'neonatology' and 'pain')		
	propofol	Short-term sedation for procedures	Data on PK, efficacy and safety; age group < 1 month.

Therapeutic field	Product	Condition(s)	Priority
Metabolism			
	alendronate	Osteoporosis induced by immobility (e.g. neuromuscular disorders), corticosteroids, in idiopathic juvenile osteoporosis, in human immunodeficiency virus (HIV) patients	Data on efficacy and short- and long-term safety (oral use).
	pamidronate	Osteoporosis induced by immobility (e.g. neuromuscular disorders), corticosteroids, in idiopathic juvenile osteoporosis, in HIV patients	Data on efficacy and short- and long-term safety (intravenous use).
Neonatology	(refer also to other fields such as 'cardiology', 'infections', 'intensive care/anaesthesiology', 'neurology', 'pain')		
	allopurinol	Cerebral neuroprotection in hypoxic ischemic encephalopathy	Proof of concept – if this is shown, data on PK, efficacy and safety for intravenous formulation.
	lidocaine	Neonatal seizures	Data on PK, efficacy and safety for intravenous formulation.
	spironolactone	Bronchopulmonary dysplasia, ascites, oedema	Data on PK, efficacy and safety. Age-appropriate formulation.
	topiramate	Neonatal seizures	Data on PK, efficacy and safety for intravenous formulation. Age-appropriate formulation.
Nephrology / urology	(refer also to 'cardiology')		
	amiloride	Nephrogenic diabetes insipidus, symptomatic treatment of nephrotic syndrome	Data on PK, efficacy and long-term safety; age-appropriate formulation.
	amlodipine	Hypertension	Data on PK, efficacy and safety, age group < 6 years; neurodevelopmental adverse reactions; age-appropriate formulation.

Therapeutic field	Product	Condition(s)	Priority
	labetalol	Hypertension	Data on PK, efficacy and safety for acute blood pressure reduction
	metoprolol	Hypertension	Data on PK, efficacy and safety.
Neurology	(refer also to 'neonatology', 'metabolism')		
	clobazam	Epilepsy syndromes	Data on PK and safety. Age-appropriate formulation
	felbamate	Epilepsy syndromes	Data on efficacy (data available only for Lennox-Gastaut syndrome) Data on PK in children below the age of 4 years
	sultiame	Epilepsy syndromes	Data on PK, safety and efficacy Age appropriate formulation
	tetrabenazine	Dystonia, movement disorders, extrapyramidal dyskinesia.	Data on PK, efficacy and safety; age-appropriate intravenous formulation.
	thiopental	Status epilepticus	Data on efficacy and safety. Comparative study in ICU patients.
	topiramate	Epilepsy syndromes	Data on efficacy (data available only for partial-onset seizures and Lennox-Gastaut syndrome)
	valproate	(1) Generalised epilepsy, (2) partial onset seizures, (3) status epilepticus	(1, 2) PK and safety for high dose treatment. PK, safety and efficacy in infants < 2 months. (3) Efficacy and safety with intravenous formulation.
Oncology	(refer also to 'immunology')		
	carboplatin	Solid tumours	Data on efficacy and long term safety in all paediatric age groups.
	daunorubicin	(1) Lymphoma, (2) acute lymphoblastic leukaemia (ALL)	(1, 2) Data on PK and efficacy in infants.

Therapeutic field	Product	Condition(s)	Priority
	etopophos	(1) Solid tumours, (2) before allogenic and autologous HSCT for various conditions	(1, 2) Data on PK, efficacy short and long term safety in all paediatric age groups. Age-appropriate oral formulation.
	fludarabine	Before allogenic HSCT for various conditions	Data on PK, short- and long-term safety; in all paediatric age groups.
	ifosfamide	(1) Nephroblastoma, lymphoma, (2) germ cell tumours, (3) neuroblastoma (4) Solid tumours and ALL	(1, 2, 3) Data on PK in children with a single kidney, long-term follow up of kidney function and evaluation of other long-term sequelae. (4) Data on PK, efficacy and (long-term) safety; need to define lower age group.
	irinotecan	Solid tumours	Data on PK in children below the age of 3 years, efficacy and safety. Age-appropriate oral formulation.
	melphalan	Before allogenic and autologous HSCT for various conditions.	Data on PK, efficacy, short- and long-term safety; in all paediatric age groups.
	thioguanine	Acute myeloid leukaemia	Data on PK, efficacy, short- and long-term safety; in all paediatric age groups ; age-appropriate oral formulation.
	vinblastine	(1) Histiocytosis, (2) Hodgkin's disease	Data on efficacy in all age groups. Age-appropriate oral formulation.
	vinorelbine	Solid tumours	Data on efficacy in all age groups. Age-appropriate oral formulation.
	topotecan	Soft-tissue and Ewing sarcoma	Data on PK and efficacy in all age groups
Anti-emetic	granisetron	Vomiting post chemotherapy, post radiation or post operative	Data on efficacy and safety; all age groups in particular from birth to less than 2 years of age.

Therapeutic field	Product	Condition(s)	Priority
Supportive	enoxaparin	Anticoagulation	Data on PK, safety and efficacy
Pain	(refer also to 'intensive care', 'neonatology')		
	carbamazepine	Chronic pain	Data on efficacy and safety.
	clonidine	Acute, chronic pain	Data on PK, efficacy and safety. Age appropriate formulations.
	ibuprofen (parenteral)	Acute, chronic pain	Data on PK, efficacy and safety (including risk of infection) of parenteral formulation.
Pneumology	(refer also to 'infections', 'immunology', 'intensive care')		
	azithromycin	(1) E.g. cystic fibrosis (CF), severe persistent asthma (2) Prevention of respiratory infection in CF and neuromuscular disorders	(1) Data on PK, anti-inflammatory efficacy, safety; all paediatric age groups. (2) Data on PK, efficacy and safety.
	dornase alfa	(1) Cystic Fibrosis (2) Primary ciliary dyskinesia, non-CF bronchiectasis	(1) Data on PK, efficacy and safety; age group below the age of 5 years. (2) Data on PK, efficacy and safety; all paediatric age groups.
	flucloxacillin	Prevention of respiratory infection in CF, neuromuscular disorders, non-CF bronchiectasis, immune deficiency	Data on PK, efficacy and safety (CF-patients identified by neonatal screening).
	hypertonic saline solution	(1) Primary ciliary dyskinesia, (2) non-CF bronchiectasis	(1, 2) Data on efficacy and safety.
	intranasal corticosteroids	Sleep-related breathing disorder	Data on PK, safety and efficacy, particularly in children < 4 years of age.
	montelukast (parenteral)	Severe post-bronchiolitis wheeze	Data on PK, safety and efficacy; iv-formulation.

Therapeutic field	Product	Condition(s)	Priority
Rheumatology	(refer also to 'immunology')		
	cyclophosphamide	Systemic lupus erythematosus, systemic vasculitides, juvenile dermatomyositis, systemic sclerosis	Data on PK, efficacy and safety.
	hydroxychloroquine	Systemic lupus erythematosus, juvenile dermatomyositis	Data on PK and safety. Age-appropriate formulation.
	ibuprofen	Juvenile idiopathic arthritis, inflammatory conditions	Data on efficacy and long-term safety.
	intravenous immunoglobulin	Juvenile dermatomyositis	Data on efficacy and safety.
	triamcinolone	Juvenile idiopathic arthritis	Data on safety and efficacy for intra-articular injection; age group < 6 years.

Abbreviations

ALL	Acute lymphoblastic leukaemia
CF	Cystic fibrosis
DM II	Diabetes mellitus Type II
HIV	Human immunodeficiency virus
HSCT	Haematopoietic stem cell transplantation
ICU	Intensive care unit
JIA	Juvenile idiopathic arthritis
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PUMA	Paediatric use marketing authorisation
TNF	Tumour necrosis factor

Methodology

The original list (2003) was prepared from a public health perspective, initially prioritising conditions based on factors such as severity of disease, non-availability of treatment alternatives, affected paediatric age groups, and paediatric prevalence data. Then, for each condition, medicinal off-patent products were identified according to published therapeutic reviews.

For the revision in 2008, medicinal products were prioritised also taking into account the WHO list of essential medicines for children, the FDA/NICHD list of products and further paediatric needs. Potential collaboration with FDA/NICHD has been taken into consideration, to avoid duplication of efforts.

The latest revisions took into account the projects which have been funded in the previous calls, as well as comments and proposals from learned scientific and paediatric societies, following a wide call for expression of interest.