Periodic report on drugs approved for children under the EU Centralised Procedure

Index

1. Abstract

This is the periodic report prepared by the TEDDY Network on paediatric medicines registered in Europe under the EMA Centralised Procedure from the beginning to October 1995 to October 2016.[i]

2. Introduction

In the pharmaceutical field the main goal is to guarantee that efficacious, high quality and safe medicines are available to European citizens, regardless of income or social status. The proper use of medicines depends on a wide dissemination of relevant information to all the interested stakeholders (regulatory agencies, medical doctors, pharmacists, patient associations, industries, etc).

For many years, a lack of information on drugs continued to affect the paediatric population. It is well known that approved medicines are used in children without proper information on: dosage, potential toxicity, evidence of clinical safety and efficacy at the recommended dosages.

The specific issue of paediatric medicines has been considered by the European Institutions since 1997. For this purpose, a number of initiatives have been developed during the last years, culminating with the entering into force of the European Paediatric Regulation [1] in January 2007.

TEDDY collects and stores in its database EPMD (European Paediatric Medicines Database) data on paediatric medicines registered in Europe under the EMA Centralised Procedure from October 1995. Reports are released regularly; two publications are available [2,3].

The aim of this report is to present the status of paediatric medicines licensed by EMA. An insight on authorisations/variations until 2016.

3. Methodology

3.1. Data collection and storing

The EMA public website represents the source of information. For each new medicine approved, including new Marketing Authorisations (MAs) and variations listed on the EMA website, the European Public Assessment Reports (EPARs) of human medicines are analysed. Information derived by EPARs is collected in a standardised way and stored in TEDDY European Paediatric Medicines Database (EPMD). Data are collected and validated by two researchers. Discrepancies are solved with the support of a supervisor.

3.2. Collected data

EPMD includes a number of information including:

- Year of approval
- Active substance
- Trade Name
- Anatomical Therapeutic Chemical (ATC) code - first-level
- Indication and Paediatric Indication

- Ages for which the drug is intended
- Dosages
- Orphan Drug status
- Paediatric trials and studies included in the EPAR at the time of approval.

3.3. Data Analysis

General descriptive statistics analyses are performed on annual basis providing details on: a) year of MA, b) age of population for which the drug is approved, c) ATC code, and d) orphan status. In addition, the database allows to perform other analyses according to specific request.

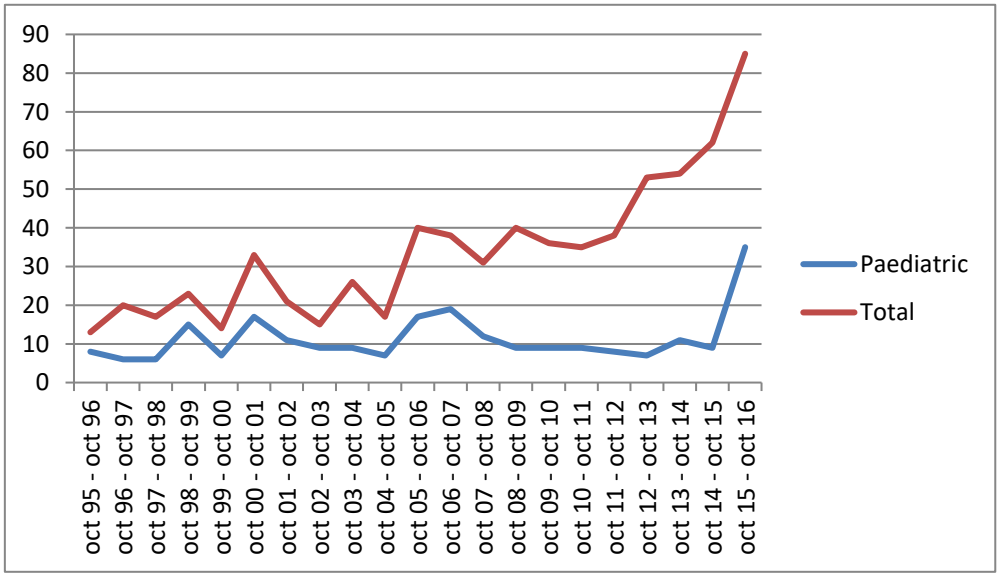
4. Results

4.1. Number and percentage of paediatric medicines

In the period October 1995 – October 2016, 674 active substances (ASs) have been approved by EMA under the Centralised Procedure: 232 of them are paediatric (34%).[1]

Figure 1 reports the number of paediatric medicines and the total of medicines approved by EMA under the centralised procedure. MAs and variations are included. Notwithstanding the increase observed in 2007, the number of paediatric medicines remains low till 2015. A new increase is observed in the period October 2015 to October 2016 (see paragraph 5)

Figure 1 - Medicinal products authorised by EMA divided by year (Oct. 1995 – Oct. 2016)

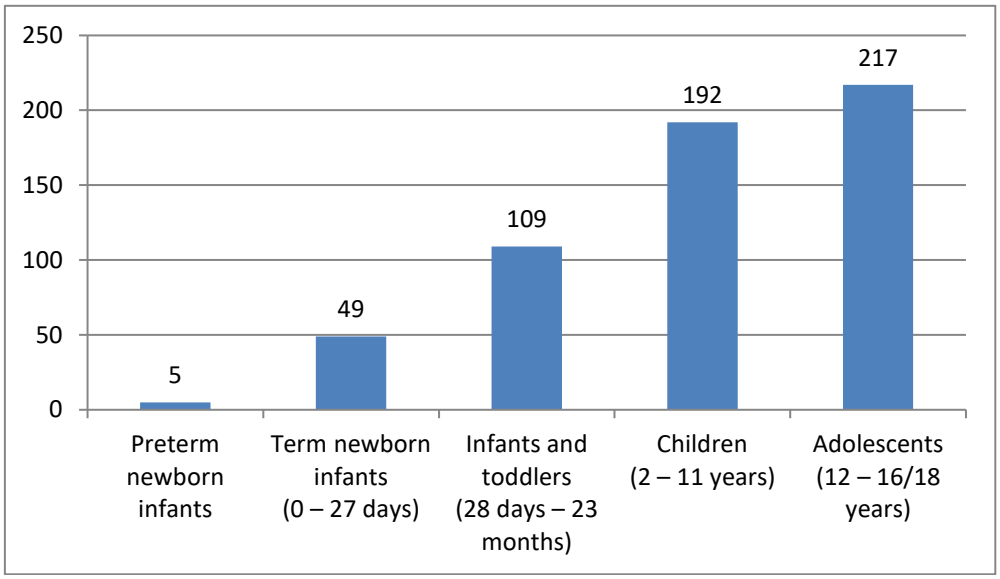


[1] In the first ten years period covered by this report (1995-2005), medicines that included in their documentation (Summary of Product Characteristics – SPC/PL) a paediatric dosages information, but not a paediatric indication, were also considered as paediatric.

4.2. Distribution of paediatric medicines by age

Figure 2 reports the distribution of the paediatric medicines by age for which the drug is approved. It is evident that the lower number of medicines refers to neonates and younger children, while this number increases for older children and is the highest for adolescents.

Figure 2 – Paediatric Medicines: age distribution



4.3. Distribution of paediatric medicines by ATC

Authorised paediatric medicines belong to 14 ATC first-level categories. The percentage of paediatric medicines for each therapeutic area significantly varies among ATC codes: J-ATC (anti-infectives for systemic use) represents the group with the highest ratio on the total of authorised medicines, while G-ATC (Genito-urinary system and sex hormones), M-ATC (Musculo-skeletal system)and P-ATC (Antiparasitic) the lowest ones. Table 1 provides additional details.

Table 1: EMA Paediatric Medicines by ATC code

	Paediatric/Total	
	N	**%**
A -Alimentary tract and metabolism	36/84	42
B - Blood and blood forming organs	22/55	40
C - Cardiovascular system	5/41	12
D - Dermatologicals	3/8	38
G- Genito-urinary system and sex hormones	1/27	4
H - Systemic hormonal preparations, excluding sex hormones and insulins	2/13	15
J - Anti-infectives for systemic use	90/135	67
L - Antineoplastic and immunomodulating agents	35/150	23

	Paediatric/Total	
	N	**%**
M - Musculo-skeletal system	1/16	6
N - Nervous system	13/57	23
P -Antiparasitic products, insecticides and repellents	1/1	100
R - Respiratory system	9/24	37
S - Sensory organs	3/20	15
V -Various	9/40	23
Not assigned yet	2/2	100
TOTAL	***232/674***	***34%***

4.4. Distribution of paediatric medicines by orphan status

With reference to orphan drugs, it should be noted that out of the 88 orphan drugs authorised by the EMA in the period October 1995 – October 2016 under the OD Regulation rules, 40 were paediatric. Thus, comparing the rate of paediatric medicines between orphan and non-orphan drug groups, a significant difference in favour of paediatric medicines in the orphan drug group is evident (45% and 34%, respectively). In particular, in some disease categories such as A, J, N, the majority of the approved orphan medicinal products are licensed for children (Table 2).

Table 2 – Paediatric orphan drugs and ATC distribution

ATC	Orphan drugs authorised	Paediatric orphan drugs authorised	Percentage
A -Alimentary tract and metabolism	13	13	100
B - Blood and blood forming organs	5	4	80
C - Cardiovascular system	5	0	-
D - Dermatologicals	2	0	-
G- Genito-urinary system and sex hormones	0	0	-
H - Systemic hormonal preparations, excluding sex hormones and insulins	3	1	33
J - Anti-infectives for systemic use	7	4	57
L - Antineoplastic and immunomodulating agents	40	10	25
M - Musculo-skeletal system	0	0	-
N - Nervous system	8	4	50
P -Antiparasitic products, insecticides and repellents	0	0	-
R - Respiratory system	2	1	50
S - Sensory organs	1	0	-
V -Various	0	1	-
Not assigned yet	2	2	100
TOTAL	**88**	**40**	***45%***

5. New paediatric drug from October 2015 to October 2016

Active substance	ATC code	Paediatric indication	Orphan	Paediatric Age	Variations
Aripiprazole (Generic)	N05AX12	Aripiprazole Accord is indicated for the treatment of schizophrenia in adults and in adolescents aged 15 years and older. Aripiprazole Accord is indicated for the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older.	NO	13 years (Bipolar I Disorder); 15 years (schizophrenia)	
efmoroctocog alfa	B02BD02	Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). ELOCTA can be used for all age groups.	NO	all ages	
lumacaftor/ivacaftor	R07AX30	Orkambi is indicated for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene.	NO	12 years	
elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide	J05AR	Genvoya is indicated for the treatment of adults and adolescents (aged 12 years and older with body weight at least 35 kg) infected with human immunodeficiency virus-1 (HIV-1) without any known mutations associated with resistance to the integrase inhibitor class, emtricitabine or tenofovir.	NO	12 years at least 35 kg	
glycerol phenylbutyrate	A16AX09	RAVICTI is indicated for use as adjunctive therapy for chronic management of adult and paediatric patients ≥2 months of age with urea cycle disorders (UCDs) including deficiencies of carbamoyl phosphate-synthase-I (CPS), ornithine carbamoyltransferase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL), arginase I (ARG) and ornithine translocase deficiency hyperornithinaemiahyperammonaemia homocitrullinuria syndrome (HHH) who cannot be managed by dietary protein restriction and/or amino acid supplementation alone. RAVICTI must be used with dietary protein restriction and, in some cases, dietary supplements (e.g. essential amino acids, arginine, citrulline, protein-free calorie supplements).	YES	2 months	
pegaspargase	L01XX24	Oncaspar is indicated as a component of antineoplastic combination therapy in acute lymphoblastic leukaemia (ALL) in paediatric patients from birth to 18 years, and adult patients.	NO	all ages	
brivaracetam	N03AX23	Briviact is indicated as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in adult and adolescent patients from 16 years of age with epilepsy.	NO	from 16 years	
asparaginase	L01XX02	Spectrila is indicated as a component of antineoplastic combination therapy for the treatment of acute lymphoblastic leukaemia (ALL) in paediatric patients from birth to 18 years and adults.	NO	all ages	

Active substance	ATC code	Paediatric indication	Orphan	Paediatric Age	Variations
lopinavir/ritonavir (Generic)	J05AR10	Lopinavir/ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infected adults, adolescents and children above the age of 2 years. The choice of lopinavir/ritonavir to treat protease inhibitor experienced HIV-1 infected patients should be based on individual viral resistance testing and treatment history of patients.	NO	2 years	
caspofungin acetate (Generic)	J02AX04	-Treatment of invasive candidiasis in adult or paediatric patients. -Treatment of invasive aspergillosis in adult or paediatric patients who are refractory to or intolerant of amphotericin B, lipid formulations of amphotericin B and/or itraconazole. Refractoriness is defined as progression of infection or failure to improve after a minimum of 7 days of prior therapeutic doses of effective antifungal therapy. -Empirical therapy for presumed fungal infections (such as Candida or Aspergillus) in febrile, neutropaenic adult or paediatric patients.	NO	from 12 months	
VACCINE Diphtheria toxoid / tetanus toxoid / Bordetella pertussis antigens: pertussis toxoid, filamentous haemagglutinin, pertactin, fimbriae Types 2 and 3 / hepatitis B surface antigen produced in yeast cells / poliovirus (inactivated): type 1 (Mahoney), type 2 (MEF-1), type 3 (Saukett) produced in Vero cells/ Haemophilus influenzae type b polysaccharide (polyribosylribitol phosphate) conjugated to meningococcal protein	J07CA09	Vaxelis (DTaP-HB-IPV-Hib) is indicated for primary and booster vaccination in infants and toddlers from the age of 6 weeks, against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and invasive diseases caused by Haemophilus influenzae type b (Hib).	NO	from 6 weeks	
octocog alfa	B02BD02	Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). Kovaltry can be used for all age groups.	NO	all ages	
octocog alfa	B02BD02	Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). Iblias can be used for all age groups.	NO	alll ages	
cholic acid	A05AA03	Kolbam, is indicated for the treatment of inborn errors in primary bile acid synthesis due to Sterol 27-hydroxylase (presenting as cerebrotendinous xanthomatosis, CTX) deficiency, 2- (or a-) methylacyl-CoA racemase (AMACR) deficiency or Cholesterol 7a-hydroxylase (CYP7A1) deficiency in infants, children and adolescents aged 1 month to 18 years and adults.	YES	1 month	

Active substance	ATC code	Paediatric indication	Orphan	Paediatric Age	Variations
rilpivirine	J05AG05	EDURANT, in combination with other antiretroviral medicinal products, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-naïve patients 12 years of age and older with a viral load ≤ 100,000 HIV-1 RNA copies/ml. As with other antiretroviral medicinal products, genotypic resistance testing should guide the use of EDURANT.	NO	12 years	22/10/2015 (20/11/2015) Extension of Indication to include treatment of antiretroviral treatment-naïve paediatric patients aged 12 to <18 years. (Update: 25/01/2016)
daptomycin	J01XX09	Cubicin is indicated for the treatment of the following infections: - Adult and paediatric (1 to 17 years of age) patients with complicated skin and soft-tissue infections (cSSTI).	NO	1 year	22/10/2015 (19/11/2015): Extension of indication to extend the age range for the indication "complicated skin and soft-tissue infections" (cSSTI), to include paediatric patients from 1 to 17 years of age. (Update: 28/01/2015)
aprepitant	A04AD12	Emend 80 mg and 125 mg hard capsules are ìndicated for the prevention of nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy in adults and adolescents from the age of 12. Emend powder for oral suspension is indicated for the prevention of nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy in children, toddlers and infants from the age of 6 months to less than 12 years. Emend is given as part of combination therapy.	NO	6 months	22/10/2015 (16/12/2015): Change(s) to therapeutic indication(s). (Update: 01/02/2016)
human coagulation factor X	B02BD13	Coagadex is indicated for the treatment and prophylaxis of bleeding episodes and for perioperative management in patients with hereditary factor X deficiency.	YES	12 years	
Zonisamide (Generic)	N03AX15	Zonisamide Mylan is indicated as: - adjunctive therapy in the treatment of partial seizures, with or without secondary generalisation, in adults, adolescents, and children aged 6 years and above.	NO	6 years	
eltrombopag olamine	B02BX05	Revolade is indicated for chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients aged 1 year and above who are refractory to other treatments (e.g. corticosteroids, immunoglobulins).	NO	1 year	28/01/2016 (04/04/2016): Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one. (Update 20/04/2016)

Active substance	ATC code	Paediatric indication	Orphan	Paediatric Age	Variations
palonosetron hydrochloride (Generic)	A04AA05	Palonosetron Hospira is indicated in paediatric patients 1 month of age and older for: • the prevention of acute nausea and vomiting associated with highly emetogenic cancer chemotherapy and prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy.	NO	1 month	
bosentan monohydrate	C02KX01	Treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients with WHO functional class III.Efficacy has been shown in:- Primary (idiopathic and familial) PAH; - PAH secondary to scleroderma without significant interstitial pulmonary disease; - PAH associated with congenital systemic-to-pulmonary shunts and Eisenmenger's physiology. Some improvements have also been shown in patients with PAH WHO functional class III. Stayveer is also indicated to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease.	NO	>1 year	
human normal immunoglobulin	J06BA	Replacement therapy in adults, children and adolescents (0-18 years) in: - Primary immunodeficiency syndromes with impaired antibody production; -Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia (CLL), in whom prophylactic antibiotics have failed or are contra-indicated; - Hypogammaglobulinaemia and recurrent bacterial infections in multiple myeloma (MM) patients; - Hypogammaglobulinaemia in patients pre- and post-allogeneic hematopoietic stem cell transplantation (HSCT).	NO	all ages	28/04/2016 (01/06/2016) Extension of indication to include paediatric population for all authorised indications (Update 16/08/2016)
emtricitabine / tenofovir alafenamide	J05AR17	Descovy is indicated in combination with other antiretroviral agents for the treatment of adults and adolescents (aged 12 years and older with body weight at least 35 kg) infected with human immunodeficiency virus type 1 (HIV-1).	NO	> 12 years at least 35 kg	
albutrepenonacog alfa	B02BD04	Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency). IDELVION can be used for all age groups.	YES	all ages	
eftrenonacog alfa	B02BD04	Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency). Alprolix can be used for all age groups.	YES	all ages	
reassortant influenza virus (live attenuated) of the following strain: A/Vietnam/1203/2004 (H5N1) strain	J07BB03	Prophylaxis of influenza in an officially declared pandemic situation in children and adolescents from 12 months to less than 18 years of age. Pandemic influenza vaccine H5N1 MedImmune should be used in accordance with official guidance.	NO	> 12 months to 18 years	
migalastat hydrochloride	not yet assigned	Galafold is indicated for long-term treatment of adults and adolescents aged 16 years and older with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency) and who have an amenable mutation.	YES	> 16 years	

Active substance	ATC code	Paediatric indication	Orphan	Paediatric Age	Variations
infliximab	L04AB02	-Paediatric Crohn's disease: Flixabi is indicated for treatment of severe, active Crohn's disease in children and adolescents aged 6 to 17 years, who have not responded to conventional therapy including a corticosteroid, an immunomodulator and primary nutrition therapy; or who are intolerant to or have contraindications for such therapies. Infliximab has been studied only in combination with conventional immunosuppressive therapy. -Paediatric ulcerative colitis: Flixabi is indicated for treatment of severely active ulcerative colitis in children and adolescents aged 6 to 17 years, who have had an inadequate response to conventional therapy including corticosteroids and 6-MP or AZA, or who are intolerant to or have medical contraindications for such therapies.	NO	6 to 17 years	
Palonosetron (Generic)	A04AA05	Palonosetron Accord is indicated in paediatric patients 1 month of age and older for the prevention of acute nausea and vomiting associated with highly emetogenic cancer chemotherapy and prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy.	NO	> 1 month	
emtricitabine / rilpivirine hydrochloride / tenofovir alafenamide	J05AR19	Treatment of adults and adolescents (aged 12 years and older with body weight at least 35 kg) infected with human immunodeficiency virus 1 (HIV 1) without known mutations associated with resistance to the non nucleoside reverse transcriptase inhibitor (NNRTI) class, tenofovir or emtricitabine and with a viral load ≤ 100,000 HIV 1 RNA copies/mL.	NO	> 12 years at least 35 kg	
pancreas powder	A09AA02	Pancreatic enzyme replacement treatment in exocrine pancreatic insufficiency due to cystic fibrosis or other conditions (e.g. chronic pancreatitis, post pancreatectomy or pancreatic cancer). Enzepi is indicated in infants, children, adolescents and adults.	NO	all ages	
methotrexate	L01BA01	Nordimet is indicated for the treatment of: polyarthritic forms of severe, active juvenile idiopathic arthritis (JIA), when the response to nonsteroidal anti-inflammatory drugs (NSAIDs) has been inadequate,	NO	> 3 years	
glycopyrronium bromide	A03AB02	Symptomatic treatment of severe sialorrhoea (chronic pathological drooling) in children and adolescents aged 3 years and older with chronic neurological disorders.	NO	> 3 years	
sildenafil citrate	G04BE03	Paediatric population Treatment of paediatric patients aged 1 year to 17 years old with pulmonary arterial hypertension. Efficacy in terms of improvement of exercise capacity or pulmonary haemodynamics has been shown in primary pulmonary hypertension and pulmonary hypertension associated with congenital heart disease.	NO	> 1 year	

6. References

1. European Parliament and Council Regulation (EC) No 1901/2006, 12 December 2006, on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004

2. Ceci A, Felisi M, Baiardi P, Bonifazi F, Catapano M, Giaquinto C, Nicolosi A, Sturkenboom M, Neubert A, Wong I. Medicines for children licensed by the European Medicines Agency (EMEA): the balance after 10 years Eur J Clin Pharmacol 2006. Nov;62(11):947-52.

3. Ceci A, Felisi M, Catapano M, Baiardi P, Cipollina L, Ravera S, Bagnulo S, Reggio S, Rondini G. Medicines for children licensed by the European Agency for the Evaluation of Medicinal Products. Eur J Clin Pharmacol. 2002 Nov;58(8):495-500.

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