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

(period: January 2022 – December 2022)

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 October 1995 to December 2022.[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.The Regulation is currently under revision by European Commission.

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; three 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 2021.

3. Methodology

3.1. Data collection and storing

The EMA public website (section "What's new") 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 on each medicinal product approved by EMA including:

- Year of approval
- Active substance
- Tradename
- Anatomical Therapeutic Chemical (ATC) code - first-level
- Indication and Paediatric Indication
- Ages for which the drug is intended

- Orphan Drug status
- Paediatric trials and studies included in the EPAR at the time of approval of the paediatric indication or variation.

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.

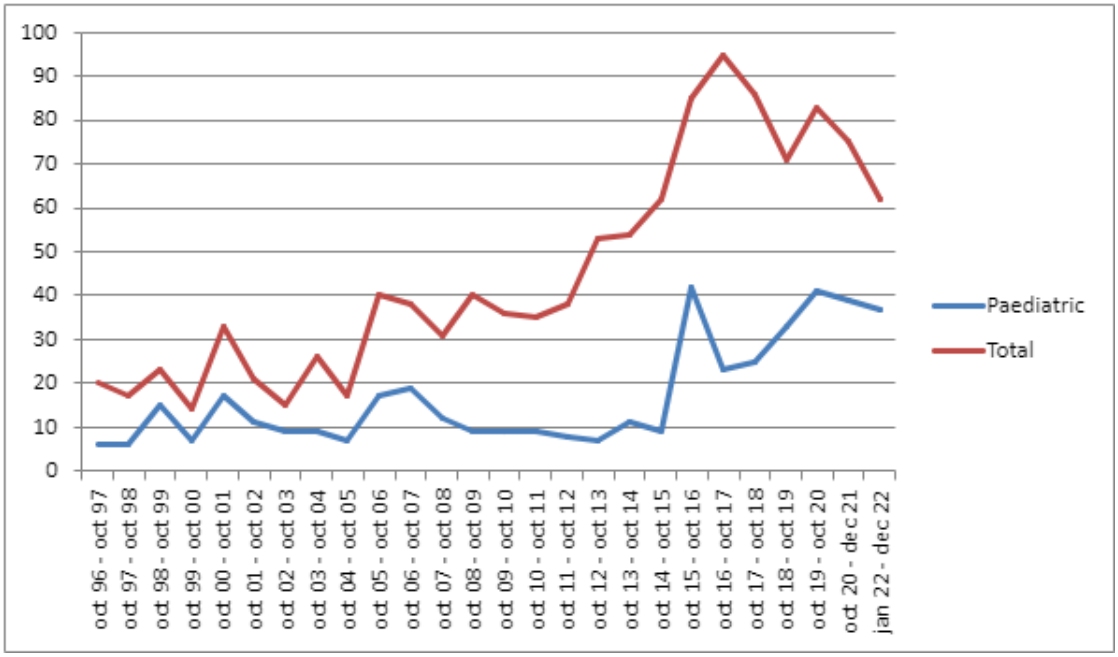
4. Results

4.1. Number and percentage of paediatric medicines

From the EMA institution to December 2022, 1003 active substances (ASs) have been approved under the Centralised Procedure: 374 of them were paediatric (37%).[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 from 2015.

Figure 1 - Medicinal products authorised by EMA divided by year (Oct. 1995 – Dec. 2022)

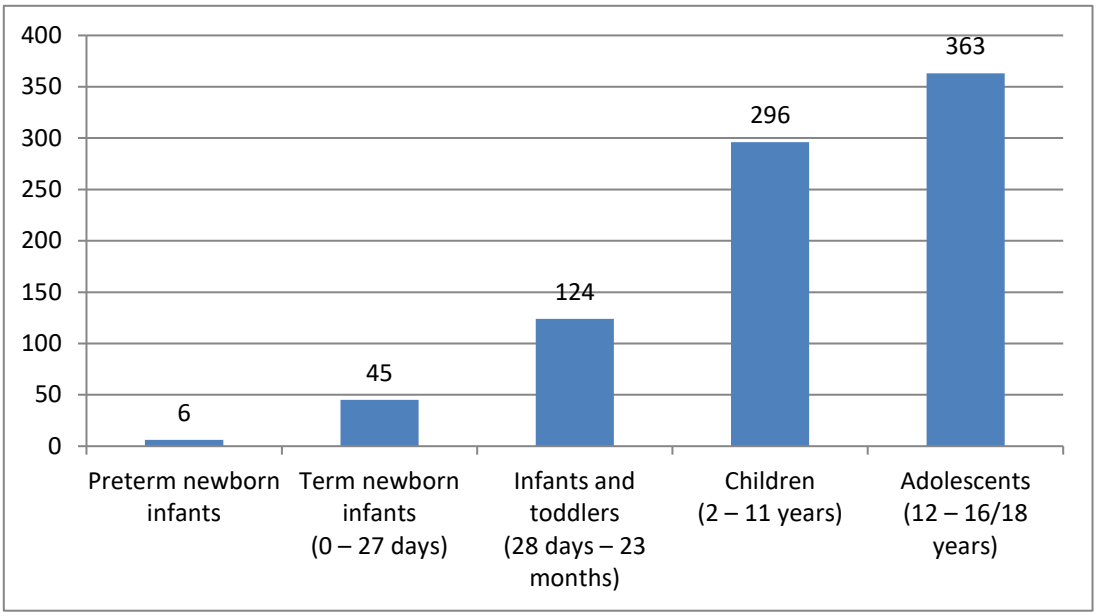


[1] In the first ten years period covered by this report (1995-2005), medicines that included in their documentation (Summary of Product Characteristics – SPC/PL) a paediatric dosages information, but not a paediatric indication, were also considered as paediatric.

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" (54%) represents the group with the highest ratio on the total of authorised medicines, followed by B-ATC "Blood and blood forming organs" (52%) and A-ATC "Alimentary tract and metabolism" (51%); C-ATC "Cardiovascular system" (17%) and G-ATC "Genito-urinary system and sex hormones" (15%) the lowest ones. Table 1 provides additional details.

Table 1: EMA Paediatric Medicines by ATC code	**Paediatric/Total**	
	N	**%**
A -Alimentary tract and metabolism	59/115	51
B - Blood and blood forming organs	38/73	52
C - Cardiovascular system	8/47	17
D - Dermatologicals	6/15	40
G - Genito-urinary system and sex hormones	5/34	15
H - Systemic hormonal preparations, excluding sex hormones and insulins	7/21	33
J - Anti-infectives for systemic use	101/188	54

Table 1: EMA Paediatric Medicines by ATC code	Paediatric/Total	
	N	%
L - Antineoplastic and immunomodulating agents	69/261	26
M - Musculo-skeletal system	7/28	25
N - Nervous system	26/84	31
P - Antiparasitic products, insecticides and repellents	2/2	100
R - Respiratory system	16/38	42
S - Sensory organs	6/28	21
V - Various	17/56	30
Not assigned yet	7/13	54
TOTAL	***374/1003***	***37%***

4.4. Distribution of paediatric medicines by orphan status

With reference to orphan drugs, it should be noted that out of the 141 orphan drugs authorised from the EMA institution to December 2022 under the OD Regulation rules, 71 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 (51% and 37%, respectively).

Table 2 – Paediatric orphan drugs and ATC distribution

ATC	Orphan medicinal products authorised	Paediatric orphan drugs authorised	Percentage
A -Alimentary tract and metabolism	24	21	87
B - Blood and blood forming organs	11	9	81
C - Cardiovascular system	3	0	-
D - Dermatologicals	3	1	33
G- Genito-urinary system and sex hormones	0	0	-
H - Systemic hormonal preparations, excluding sex hormones and insulins	6	2	33
J - Anti-infectives for systemic use	12	6	50
L - Antineoplastic and immunomodulating agents	48	10	21
M - Musculo-skeletal system	6	5	83
N - Nervous system	11	7	64
P -Antiparasitic products, insecticides and repellents	1	1	100
R - Respiratory system	2	2	100
S - Sensory organs	4	2	50
V -Various	3	1	33
Not assigned yet	7	4	57
TOTAL	**141**	**71**	***51%***

5. New paediatric drug from January 2022 to December 2022

Active substance	ATC code	Paediatric indication	Orphan	Paediatric Age	Variations	PIP
artesunate	P01BE03	**Artesunate Amivas** is indicated for the initial treatment of severe malaria in adults and children	YES	all ages		YES
dapagliflozin	A10BK01	Type 2 diabetes mellitus: **Forxiga** is indicated in adults and children aged 10 years and above for the treatment of insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise - as monotherapy when metformin is considered inappropriate due to intolerance. - in addition to other medicinal products for the treatment of type 2 diabetes.	NO	> 10 years	14/10/21 (15/11/21): Extension of indication for Forxiga / Edistride to include treatment of children aged 10 years and adolescents with T2DM based on the results from studies MB10209/D1690C000016 and MB102-138/D1690C00017; these are paediatric studies submitted according to Article 46 of the Paediatric Regulation	YES
Adalimumab (biosimilar)	L04AB04	Juvenile idiopathic arthritis**:** **Libmyris** in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in patients from the age of 2 years who have had an inadequate response to one or more DMARD. Libmyris can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate (for the efficacy in monotherapy see section 5.1). Adalimumab has not been studied in patients aged less than 2 years. Enthesitis-related arthritis**:** Libmyris is indicated for the treatment of active enthesitis-related arthritis in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy. Paediatric plaque psoriasis**:** Libmyris is indicated for the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies. Hidradenitis suppurativa (HS): Libmyris is indicated for the treatment of active moderate to severe HS (acne inversa) in adults and adolescents from 12 years of age with an inadequate response to conventional systemic HS therapy. Paediatric Crohn's disease**:** Libmyris is indicated for the treatment of moderately to severely active Crohn's disease in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy and a corticosteroid and/or an immunomodulator, or who are intolerant to or have contraindications for such therapies. Paediatric ulcerative colitis**:** Libmyris is indicated for the treatment of moderately to severely active ulcerative colitis in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy including corticosteroids and/or 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies. Paediatric uveitis**:** Libmyris is indicated for the treatment of paediatric chronic non-infectious anterior uveitis in patients from 2 years of age who have had an inadequate response to or are	NO	> 2 years > 4 years > 6 years > 12 years		NO

Active substance	ATC code	Paediatric indication	Orphan	Paediatric Age	Variations	PIP
		intolerant to conventional therapy, or in whom conventional therapy is inappropriate.				
Adalimumab (biosimilar)	L04AB04	Juvenile idiopathic arthritis: Polyarticular juvenile idiopathic arthritis: **Hukyndra** in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in patients from the age of 2 years who have had an inadequate response to one or more DMARD. Hukyndra can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate (for the efficacy in monotherapy see section 5.1). Adalimumab has not been studied in patients aged less than 2 years. Enthesitis-related arthritis: Hukyndra is indicated for the treatment of active enthesitis-related arthritis in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy. Paediatric plaque psoriasis: Hukyndra is indicated for the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies. Hidradenitis suppurativa (HS): Hukyndra is indicated for the treatment of active moderate to severe HS (acne inversa) in adults and adolescents from 12 years of age with an inadequate response to conventional systemic HS therapy. Paediatric Crohn's disease: Hukyndra is indicated for the treatment of moderately to severely active Crohn's disease in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy and a corticosteroid and/or an immunomodulator, or who are intolerant to or have contraindications for such therapies. Paediatric ulcerative colitis: Hukyndra is indicated for the treatment of moderately to severely active ulcerative colitis in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy including corticosteroids and/or 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies. Paediatric uveitis: Hukyndra is indicated for the treatment of paediatric chronic non-infectious anterior uveitis in patients from 2 years of age who have had an inadequate response to or are intolerant to conventional therapy, or in whom conventional therapy is inappropriate.	NO	> 2 years > 4 years > 6 years > 12 years		NO
glucarpidase	V03AF09	**Voraxaze** is indicated to reduce toxic plasma methotrexate concentration in adults and children (aged 28 days and older) with delayed methotrexate elimination or at risk of methotrexate toxicity.	YES	> 28 days		YES
dapagliflozin propanediol monohydrate	A10BK01	Type 2 diabetes mellitus: **Edistride** is indicated in adults and children aged 10 years and above for the treatment of insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise - as monotherapy when metformin is considered inappropriate due to intolerance. - in addition to other medicinal products for the treatment of type 2 diabetes.	NO	> 10 years	14/10/21 (12/11/21): Extension of indication for Forxiga / Edistride to include treatment of children aged 10 years and adolescents with T2DM based on the results from studies MB10209/D1690C000016 and MB102-	NO

Active substance	ATC code	Paediatric indication	Orphan	Paediatric Age	Variations	PIP
					138/D1690C00017; these are paediatric studies submitted according to Article 46 of the Paediatric Regulation.	
posaconazole	J02AC04	**Noxafil** gastro-resistant tablets, are indicated for use in the treatment of the following fungal infections in paediatric patients from 2 years of age weighing more than 40 kg and adults Noxafil concentrate for solution for infusion and gastro-resistant powder and solvent for oral suspension is indicated for use in the treatment of the following fungal infections in adult and paediatric patients from 2 years of age - Invasive aspergillosis in patients with disease that is refractory to amphotericin B or itraconazole or in patients who are intolerant of these medicinal products; - Fusariosis in patients with disease that is refractory to amphotericin B or in patients who are intolerant of amphotericin B; - Chromoblastomycosis and mycetoma in patients with disease that is refractory to itraconazole or in patients who are intolerant of itraconazole; - Coccidioidomycosis in patients with disease that is refractory to amphotericin B, itraconazole or fluconazole or in patients who are intolerant of these medicinal products. 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. Noxafil gastro-resistant tablets are also indicated for prophylaxis of invasive fungal infections in the following paediatric patients from 2 years of age weighing more than 40 kg and adults Noxafil concentrate for solution for infusion and gastro-resistant powder and solvent for oral suspension is indicated for use in the treatment of the following fungal infections in adult and paediatric patients from 2 years of age - Patients receiving remission-induction chemotherapy for acute myelogenous leukaemia (AML) or myelodysplastic syndromes (MDS) expected to result in prolonged neutropenia and who are at high-risk of developing invasive fungal infections; - Hematopoietic stem cell transplant (HSCT) recipients who are undergoing high-dose immunosuppressive therapy for graft versus host disease and who are at high-risk of developing invasive fungal infections.	NO	> 2 years	11/11/21 (06/01/22): Extension application to introduce a new pharmaceutical form (gastro-resistant powder and solvent for oral suspension), grouped with a type II variation (C.I.6.a) to extend the approved indications for Noxafil to the paediatric population.	YES
Tecovirimat	J05AX24	**Tecovirimat SIGA** is indicated for the treatment of the following viral infections in adults and children with body weight at least 13 kg: o Smallpox o Monkeypox o Cowpox Tecovirimat SIGA is also indicated to treat complications due to replication of vaccinia virus following vaccination against smallpox in adults and children with body weight at least 13 kg	NO	children at least 13 kg		YES
Lonapegsomatropin	H01AC	**Skytrofa**: Growth failure in children and adolescents aged from 3 years up to 18 years due to insufficient endogenous growth hormone secretion (growth hormone deficiency [GHD])	YES	> 3 years		YES

Active substance	ATC code	Paediatric indication	Orphan	Paediatric Age	Variations	PIP
elbasvir / grazoprevir	J05AP54	**ZEPATIER** is indicated for the treatment of chronic hepatitis C (CHC) in adult and paediatric patients 12 years of age and older who weigh at least 30 kg. For hepatitis C virus (HCV) genotype-specific activity see sections 4.4 and 5.1.	NO	> 12 years weighting 30 kg	16/09/21 (22/10/21): Extension of indication to include treatment of chronic hepatitis C (CHC) in paediatric patients 12 years of age and older who weigh at least 30 kg for Zepatier	YES
somatrogon	H01AC08	**Ngenla** is indicated for the treatment of children and adolescents from 3 years of age with growth disturbance due to insufficient secretion of growth hormone.	YES	> 3 years		YES
Voxelotor	B06AX03	**Oxbryta** is indicated for the treatment of haemolytic anaemia due to sickle cell disease (SCD) in adults and paediatric patients 12 years of age and older as monotherapy or in combination with hydroxycarbamide.	YES	>12 years		YES
Rivaroxaban (generic)	B01AF01	**Rivaroxaban Accord** Paediatric population: Treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in children and adolescents aged less than 18 years and weighing from 30 kg to 50 kg after at least 5 days of initial parenteral anticoagulation treatment	NO	children from 30 kg		NO
Dasatinib (generic)	L01EA02	**Dasatinib Accordpharma** is indicated for the treatment of paediatric patients with: § newly diagnosed Ph+ CML in chronic phase (Ph+ CML-CP) or Ph+ CML-CP resistant or intolerant to prior therapy including imatinib. § newly diagnosed Ph+ ALL in combination with chemotherapy.	NO	> 1 year		NO
Dasatinib (generic)	L01EA02	**Dasatinib Accord** is indicated for the treatment of paediatric patients with: § newly diagnosed Ph+ ALL in combination with chemotherapy.	NO	> 1 year		NO
Sapropterin (generic)	A16AX07	**Sapropterin Dipharma** is indicated for the treatment of hyperphenylalaninaemia (HPA) in adults and paediatric patients of all ages with phenylketonuria (PKU) who have been shown to be responsive to such treatment. Sapropterin Dipharma is also indicated for the treatment of hyperphenylalaninaemia (HPA) in adults and paediatric patients of all ages with tetrahydrobiopterin (BH4) deficiency who have been shown to be responsive to such treatment.	NO	all ages		NO
doravirine/lamivudine/tenofovir disoproxil fumarate	J05AR	**Delstrigo** is also indicated for the treatment of adolescents aged 12 years and older weighing at least 35 kg who are infected with HIV-1 without past or present evidence of resistance to the NNRTI class, lamivudine, or tenofovir and who have experienced toxicities which preclude the use of other regimens that do not contain tenofovir disoproxil	NO	> 12 years at least 35 kg	24/02/22 (28/03/22): Extension of indication to include the new indication to the paediatric population weighing at least 35 kgs for PIFELTRO and DELSTRIGO	YES
doravirine	J05AG06	**Pifeltro** is indicated, in combination with other antiretroviral medicinal products, for the treatment of adults, and adolescents aged 12 years and older weighing at least 35 kg infected with HIV-1 without past or present evidence of resistance to the NNRTI class	NO	> 12 years at least 35 kg	24/02/22 (28/03/22): Extension of indication to include the new indication to the paediatric population weighing at least 35 kgs for PIFELTRO and DELSTRIGO	YES
tixagevimab/cilgavimab	Not yet assigned	Pre-exposure prophylaxis **EVUSHELD** is indicated for the pre-exposure prophylaxis of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40 kg. Treatment EVUSHELD is indicated for the treatment of adults and adolescents (aged 12 years and older weighing at least 40 kg) with COVID-19, who do not require	NO	> 12 years at least 40 kg	15/09/22 (16/09/22): Extension of indication to include treatment of adults and adolescents (aged 12 years and older weighing at least 40 kg) with COVID-19, who do not require supplemental oxygen and	YES

Active substance	ATC code	Paediatric indication	Orphan	Paediatric Age	Variations	PIP
		supplemental oxygen and who are at increased risk of progressing to severe COVID-19			are at increased risk of progressing to severe COVID-19	
ruxolitinib	L01EJ01	Graft versus host disease (GvHD): **Jakavi** is indicated for the treatment of patients aged 12 years and older with acute graft versus host disease or chronic graft versus host disease who have inadequate response to corticosteroids or other systemic therapies.	NO	> 12 years	24/03/22 (29/04/22): Extension of indication to include treatment of patients with acute and chronic GvHD aged 12 years and older who have inadequate response to corticosteroids or other systemic therapies for Jakavi;	YES
dimethyl fumarate	L04AX07	**Tecfidera** is indicated for the treatment of adult and paediatric patients aged 13 years and older with relapsing remitting multiple sclerosis (RRMS).	NO	> 13 years	22/04/22 (13/05/22): (Extension of indication) type II Art.29 Extension of indication to include treatment of relapsing remitting multiple sclerosis (RRMS) in paediatrics patients from 13 years of age and over	YES
pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted)	J07BB02	Prophylaxis of influenza in an officially declared pandemic situation. **Adjupanrix** should be used in accordance with official guidance	NO	> 6 months	22/04/22 (24/05/22): Extension of indication to include use in children from 6 months to <18 years for Adjupanrix based on the results of the studies: study H5N1-013, a phase II, non-randomized, open-label study to evaluate the safety and immunogenicity in children aged 6 to 35 months and study H5N1-032, a phase III, randomized, open, active-controlled study to evaluate the safety and immunogenicity in children aged 3 to 17 years.	NO
lutetium (177 Lu) chloride	V10	**Lumark** is a radiopharmaceutical precursor. It is not intended for direct use in patients. It must be used only for the radiolabelling of carrier molecules, which have been specifically developed and authorised for radiolabelling with this radionuclide	NO	children		NO
insulin aspart	A10AD05	**Truvelog Mix 30** is indicated for treatment of diabetes mellitus in adults, adolescents and children aged 10 years and above.	NO	> 10 years		NO
birch bark extract	D03AX13	**Filsuvez** Treatment of partial thickness wounds associated with dystrophic and junctional epidermolysis bullosa (EB) in patients 6 months and older.	YES	> 6 months		YES
insulin human (rDNA) (biosimilar)	A10AB01	Inpremzia is indicated for the treatment of diabetes mellitus.	NO	children		NO
corifollitropin alfa	G03GA09	**Elonva** is indicated for the treatment of adolescent males (14 years and older) with hypogonadotropic hypogonadism, in combination with human Chorionic Gonadotropin (hCG).	NO	> 14 years	22/04/22 (21/06/22): Extension of indication to include treatment of adolescent males (14 years and older) with hypogonadotropic hypogonadism, in combination with human Chorionic Gonadotropin (hCG) for Elonva, based on final results of the paediatric study P043.	YES

Active substance	ATC code	Paediatric indication	Orphan	Paediatric Age	Variations	PIP
COVID-19 Vaccine (recombinant, adjuvanted)	J07BX03	**Nuvaxovid** is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older	NO	> 12 years	23/06/22 (01/07/22): Extension of indication to include use in adolescents 12 to 17 years of age for Nuvaxovid, based on data from study 2019nCoV-301, a Phase 3, Randomized, Observer-Blinded, Placebo-Controlled Study to evaluate the efficacy, safety, and immunogenicity of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine (SARS-CoV-2 rS) with Matrix-M Adjuvant in Adult Participants ≥ 18 Years with a Pediatric Expansion in Adolescents (12 to < 18 Years)	YES
Sugammadex (generic)	V03AB35	**Sugammadex Fresenius Kabi** Reversal of neuromuscular blockade induced by rocuronium or vecuronium in adults. For the paediatric population: sugammadex is only recommended for routine reversal of rocuronium induced blockade in children and adolescents aged 2 to 17 years.	NO	> 2 years		NO
Avalglucosidase alfa	A16	**Nexviadyme** (avalglucosidase alfa) is indicated for long-term enzyme replacement therapy for the treatment of patients with Pompe disease (acid α-glucosidase deficiency).	YES	> 6 months		YES
Olipudase alfa	A16AB	**Xenpozyme** is indicated as an enzyme replacement therapy for the treatment of non-Central Nervous System (CNS) manifestations of Acid Sphingomyelinase Deficiency (ASMD) in paediatric and adult patients with type A/B or type B.	YES	all ages		YES
Betaine (generic)	A16AA06	**Amversio** is indicated as adjunctive treatment of homocystinuria, involving deficiencies or defects in: • cystathionine beta-synthase (CBS), • 5,10-methylene-tetrahydrofolate reductase (MTHFR), • cobalamin cofactor metabolism (cbl). Amversio should be used as supplement to other therapies such as vitamin B6 (pyridoxine), vitamin B12 (cobalamin), folate and a specific diet	NO	children		NO
exenatide	A10BJ01	**Bydureon** is indicated in adults, adolescents and children aged 10 years and above with type 2 diabetes mellitus to improve glycaemic control in combination with other glucose-lowering medicinal products including basal insulin, when the therapy in use, together with diet and exercise, does not provide adequate glycaemic control.	NO	> 10 years	22/04/22 (30/05/22): Extension of indication to include the treatment of adolescents and children aged 10 years and above based on the results from Study BCB114 (D5551C00002); a phase 3, double-blind, placebo-controlled, randomized, multi-center study to assess the safety and efficacy of exenatide once weekly in adolescents with type 2 diabetes, which was initially submitted and assessed by the CHMP as part of the postauthorisation measure (PAM) P46 028.	YES
lonafarnib	Not yet assigned	**Zokinvy** is indicated for the treatment of patients 12 months of age and older with a genetically confirmed diagnosis of Hutchinson-Gilford progeria	YES	> 12 months		YES

Active substance	ATC code	Paediatric indication	Orphan	Paediatric Age	Variations	PIP
		syndrome or a processing-deficient progeroid laminopathy associated with either a heterozygous LMNA mutation with progerin-like protein accumulation or a homozygous or compound heterozygous ZMPSTE24 mutation				
lipegfilgrastim	L03AA14	**Lonquex** is indicated in adults and in children 2 years of age and older for reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).	NO	> 2 years	23/06/22 (22/07/22): Extension of indication to include treatment of the paediatric population for Lonquex and introduction of an age appropriate presentation in vials	YES
eladocagene exuparvovec	N07	**Upstaza** is indicated for the treatment of patients aged 18 months and older with a clinical, molecular, and genetically confirmed diagnosis of aromatic L-amino acid decarboxylase (AADC) deficiency with a severe phenotype	YES	> 18 months		YES
ceftolozane sulfate tazobactam sodium	J01	**Zerbaxa** is indicated for the treatment of the following infections in adult and paediatric patients: - Complicated intra-abdominal infections; - Acute pyelonephritis; - Complicated urinary tract infections.	NO	All ages	23/06/22 (25/07/22): Extension of indication to include treatment of paediatric patients aged birth to less than 18 years for Zerbaxa, based on final results from studies MK-7625A-034 (A Phase 2, Randomized, Active Comparato rControlled, Double-Blind Clinical Trial to Study the Safety and Efficacy of Ceftolozane/ Tazobactam Versus Meropenem in Paediatric Subjects with Complicated Urinary Tract Infection and Acute Pyelonephritis) and MK-7625A-035 (A Phase 2, Randomized, Active Comparator-Controlled, Double-Blind Clinical Trial to Study the Safety and Efficacy of Ceftolozane/ Tazobactam Plus Metronidazole Versus Meropenem in Paediatric Subjects with Complicated Intra-Abdominal Infection)	YES
nivolumab / Relatlimab	L01XY03	**Opdualag** is indicated for the first-line treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older with tumour cell PD-L1 expression < 1%.	NO	> 12 years		YES
tezepelumab	R03DX	**Tezspire** is indicated as an add-on maintenance treatment in adults and adolescents 12 years and older with severe asthma who are inadequately controlled despite high dose inhaled corticosteroids plus another medicinal product for maintenance treatment.	NO	> 12 years		YES
lutetium (177Lu) chloride	V10X	ilLuzyce is a radiopharmaceutical precursor, and it is not intended for direct use in patients. It is to be used only for the radiolabelling of carrier molecules that have been specifically developed and authorised for radiolabelling with lutetium (177Lu) chloride.	NO	children		NO
Ertapenem (generic)	Not yet assigned	Treatment **Ertapenem SUN** is indicated in paediatric patients (3 months to 17 years of age) and in adults for the treatment of the following infections when caused by bacteria known or very likely to be susceptible to	NO	> 3 months		NO

Active substance	ATC code	Paediatric indication	Orphan	Paediatric Age	Variations	PIP
		ertapenem and when parenteral therapy is required: • Intra-abdominal infections • Community acquired pneumonia • Acute gynaecological infections • Diabetic foot infections of the skin and soft tissue				
fosdenopterin	A16AX19	**NULIBRY** is indicated for the treatment of patients with molybdenum cofactor deficiency (MoCD) Type A.	YES	> 1 year		YES
Teriflunomide (generic)	L04AA31	**Teriflunomide Accord** is indicated for the treatment of adult patients and paediatric patients aged 10 years and older with relapsing remitting multiple sclerosis (MS)	NO	> 10 years		NO
bupivacaine	N01BB01	**EXPAREL** liposomal is indicated: • in adults as a brachial plexus block or femoral nerve block for treatment of post-operative pain. • in adults and children aged 6 years or older as a field block for treatment of somatic postoperative pain from small- to medium-sized surgical wounds.	NO	> 6 years	15/9/22 (7/11/22): Extension of indication to include treatment of children aged 6 and older as a field block for treatment of somatic post-operative pain from smallto medium-sized surgical wounds for EXPAREL liposomal	YES
nirsevimab	J07B	**Beyfortus** is indicated for the prevention of Respiratory Syncytial Virus (RSV) lower respiratory tract disease in neonates and infants during their first RSV season.	NO	0-2 years		YES
Teriflunomide (generic)	L04AA31	**Teriflunomide Mylan** is indicated for the treatment of adult patients and paediatric patients aged 10 years and older with relapsing remitting multiple sclerosis (MS) (please refer to section 5.1 for important information on the population for which efficacy has been established).	NO	> 10 years		NO
tralokinumab	D11	**Adtralza** is indicated for the treatment of moderate-to-severe atopic dermatitis in adult and adolescent patients 12 years and older who are candidates for systemic therapy.	NO	> 12 years	15/09/22 (14/10/22): Extension of indication to include treatment of adolescent patients (12-17 years) for Adtralza basedon final study LP0162-1334 (ECZTRA 6): a multicentre, randomised, double-blind, placebocontrolled study in adolescent patients 12 to 17 years of age with moderate-to-severe atopic dermatitis to evaluate the efficacy and safety of tralokinumab monotherapy in this population group	YES
Bictegravir emtricitabine tenofovir alafenamide fumarate	J05AR20	**Biktarvy** is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and paediatric patients at least 2 years of age and weighing at least 14 kg without present or past evidence of viral resistance to the integrase inhibitor class, emtricitabine or tenofovir	NO	> 2 years	15/09/22 (21/11/22): The MAH applied for an extension application to introduce a new strength (30 mg/120 mg/15 mg filmcoated tablets). The extension application is grouped with a type II variation (C.I.6.a) to include treatment of human immunodeficiency virus-1 (HIV-1) infection in paediatric patients at least 2 years of age and weighing at least 14 kg without present or past evidence of	YES

Active substance	ATC code	Paediatric indication	Orphan	Paediatric Age	Variations	PIP
					viral resistance to the integrase inhibitor class, emtricitabine or tenofovir	
Eptacog beta (activated)	B02BD08	**CEVENFACTA** is indicated in adults and adolescents (12 years of age and older) for the treatment of bleeding episodes and for the prevention of bleeding in those undergoing surgery or invasive procedures in the following patient groups: • in patients with congenital haemophilia with high-responding inhibitors to coagulation factors VIII or IX (i.e. ≥5 Bethesda Units (BU)) • in patients with congenital haemophilia with low titre inhibitors (BU <5), but expected to have a high anamnestic response to factor VIII or factor IX administration or expected to be refractory to increased dosing of FVIII or FIX.	NO	> 12 years		YES
pneumococcal polysaccharide conjugate vaccine (adsorbed)	J07AL02	**Vaxneuvance** is indicated for active immunisation for the prevention of invasive disease, pneumonia and acute otitis media caused by Streptococcus pneumoniae in infants, children and adolescents from 6 weeks to less than 18 years of age.	NO	> 6 week	15/09/22 (21/10/22): Extension of indication to include treatment of infants, children and adolescents from 6 weeks to less than 18 years of age for active immunisation for the prevention of invasive disease, pneumonia and acute otitis media for Vaxneuvance	YES
crizotinib	L01ED01	**XALKORI** as monotherapy is indicated for: · The treatment of paediatric patients (age ≥6 to <18 years) with relapsed or refractory systemic anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL) · The treatment of paediatric patients (age ≥6 to <18 years) with recurrent or refractory anaplastic lymphoma kinase (ALK)-positive unresectable inflammatory myofibroblastic tumour (IMT)	NO	> 6 years	15/09/22 (28/10/22): Extension of indication to include treatment of paediatric patients (age ≥ 6 to < 18 years) with relapsed or refractory systemic anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL) and with recurrent, or refractory ALK-positive unresectable inflammatory myofibroblastic tumour (IMT) for Xalkori based on the results from Studies ADVL0912 and A8081013	YES
Dimethyl fumarate (Generic)	L04AX07	**Dimethyl fumarate Mylan** is indicated for the treatment of adult and paediatric patients aged 13 years and older with relapsing remitting multiple sclerosis (RRMS).	NO	> 13 years		NO
Dimethyl fumarate (Generic)	L04AX07	**Dimethyl fumarate Polpharma** is indicated for the treatment of adult and paediatric patients aged 13 years and older with relapsing remitting multiple sclerosis (RRMS).	NO	> 13 years		NO
Dimethyl fumarate (Generic)	L04AX07	**Dimethyl fumarate Teva** is indicated for the treatment of adult and paediatric patients aged 13 years and older with relapsing remitting multiple sclerosis (RRMS).	NO	> 13 years		NO
Maralixibat chloride	A05AX04	**Livmarli** is indicated for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) 2 months of age and older	YES	> 2 months		YES
dalbavancin	J01XA04	**Xydalba** is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults and paediatric patients aged 3 months and older	NO	> 3 months		YES
dengue tetravalent vaccine (live, attenuated)	J07BX04	**Qdenga** is indicated for the prevention of dengue disease in individuals from 4 years of age.	NO	> 4 years		YES

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. Toma M, Felisi M, Bonifazi D, Bonifazi F, Giannuzzi V, Reggiardo G, de Wildt S, Ceci A and al. Paediatric Medicines in Europe: The Paediatric Regulation – Is It Time for Reform? Front. Med., 02 February 2021 Vol.8 https://doi.org/10.3389/fmed.2021.593281

3. 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.

4. 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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