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 2019.[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 2019.

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
- Tradename
- 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.

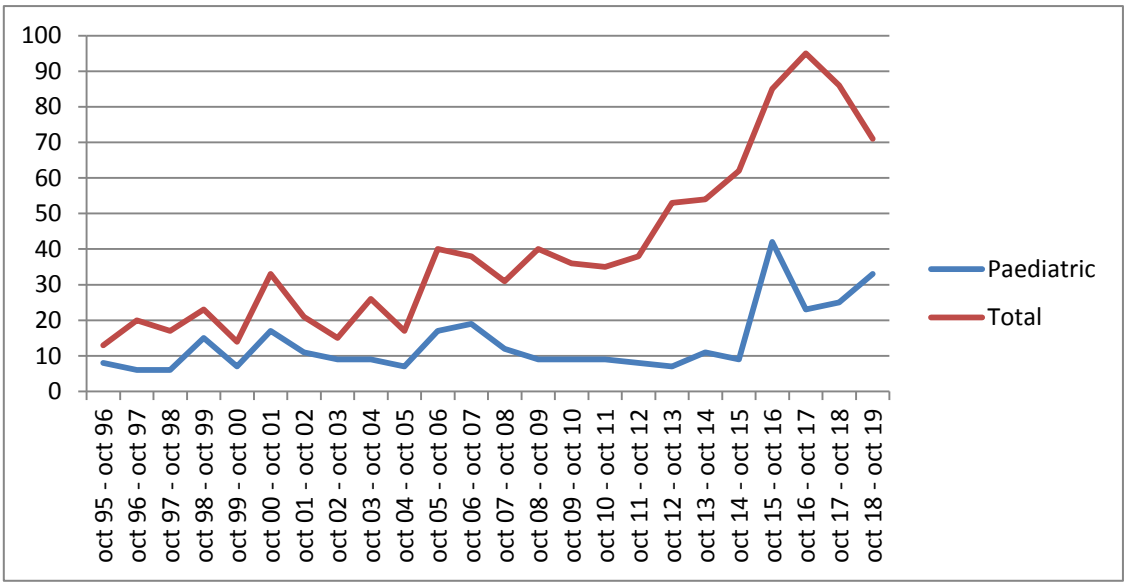
4. Results

4.1. Number and percentage of paediatric medicines

In the period October 1995 – October 2019, 829 active substances (ASs) have been approved by EMA under the Centralised Procedure: 273 of them were paediatric (33%).[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 – Oct. 2019)

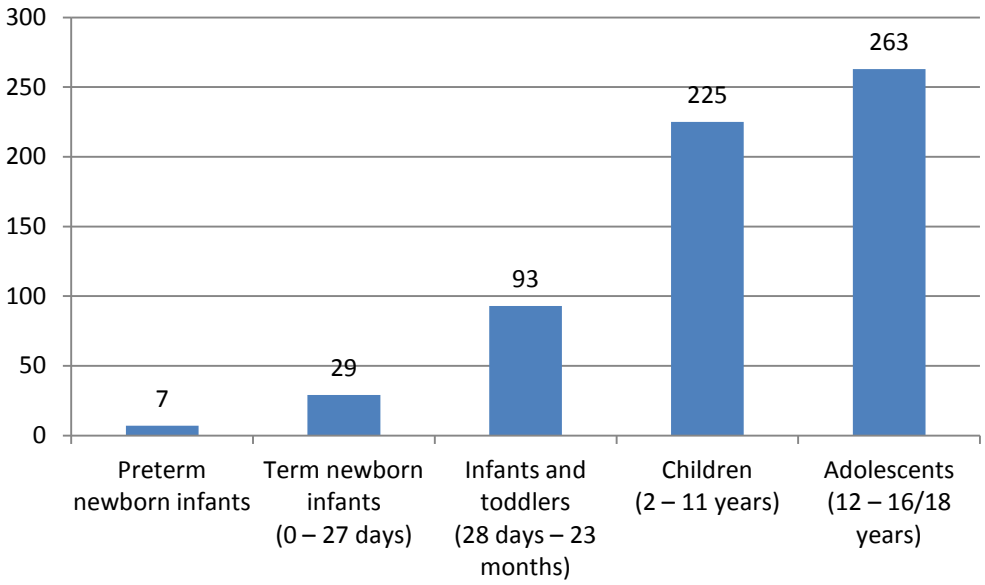


[1] In the first ten years period covered by this report (1995-2005), medicines that included in their documentation (Summary of Product Characteristics – SPC/PL) a paediatric dosages information, but not a paediatric indication, were also considered as paediatric.

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 D-ATC (**D** – Dermatologicals), G-ATC (Genito-urinary system and sex hormones), 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	48/103	47
B - Blood and blood forming organs	31/67	46
C - Cardiovascular system	6/40	15
D - Dermatologicals	3/10	30
G- Genito-urinary system and sex hormones	2/32	6
H - Systemic hormonal preparations, excluding sex hormones and insulins	4/14	29

	Paediatric / Total	
	N	**%**
J - Anti-infectives for systemic use	76/153	50
L - Antineoplastic and immunomodulating agents	51/201	25
M - Musculo-skeletal system	3/24	13
N - Nervous system	19/69	28
P -Antiparasitic products, insecticides and repellents	1/1	100
R - Respiratory system	10/29	34
S - Sensory organs	6/24	25
V -Various	12/50	24
Not assigned yet	1/12	8
TOTAL	***273/829***	***33%***

4.4. Distribution of paediatric medicines by orphan status

With reference to orphan drugs, it should be noted that out of the 132 orphan drugs authorised by the EMA in the period October 1995 – October 2019 under the OD Regulation rules, 60 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 33%, respectively).

Table 2 – Paediatric orphan drugs and ATC distribution

ATC	Orphan drugs authorised	Paediatric orphan drugs authorised	Percentage
A -Alimentary tract and metabolism	26	21	81
B - Blood and blood forming organs	8	6	75
C - Cardiovascular system	7	1	14
D - Dermatologicals	2	0	-
G- Genito-urinary system and sex hormones	0	0	-
H - Systemic hormonal preparations, excluding sex hormones and insulins	5	0	-
J - Anti-infectives for systemic use	7	4	57
L - Antineoplastic and immunomodulating agents	50	15	30
M - Musculo-skeletal system	2	2	100
N - Nervous system	11	5	45
P -Antiparasitic products, insecticides and repellents	0	0	-
R - Respiratory system	3	2	67
S - Sensory organs	4	2	50
V -Various	3	1	33
Not assigned yet	4	1	25
TOTAL	**132**	**60**	***45%***

5. New paediatric drug from October 2018 to October 2019

Active substance	ATC code	Paediatric indication	Orphan	Paediatric Age	Variations
lanadelumab	B06AC05	Takhzyro is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 12 years and older.	YES	> 12 years	
buprenorphine	N07BC01	Treatment of opioid dependence within a framework of medical, social and psychological treatment. Treatment is intended for use in adults and adolescents aged 16 years or over.	NO	> 16 years	
fingolimod hydrochloride	L04AA27	Gilenya is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following groups of adult patients and paediatric patients aged 10 years and older: - Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy (for exceptions and information about washout periods see sections 4.4 and 5.1). or - Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.	NO	> 10 years	20/09/18 (22/11/18): Gilenya is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following groups of adult patients and paediatric patients aged 10 years and older:- Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy (for exceptions and information about washout periods see sections 4.4 and 5.1). or - Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.
dengue tetravalent vaccine (live, attenuated)	J07BX	Dengvaxia is indicated for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4 in individuals 9 to 45 years of age with prior dengue virus infection and living in endemic areas. The use of Dengvaxia should be in accordance with official recommendations.	NO	> 9 years	
influenza vaccine surface antigen inactivated prepared in cell cultures	J07BB02	Prophylaxis of influenza in adults and children from 9 years of age. Flucelvax Tetra should be used in accordance with official recommendations.	NO	> 9 years	
voretigene neparvovec		Luxturna is indicated for the treatment of adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations and who have sufficient viable retinal cells.	YES	> 4 years	
Damoctocog alfa pego	B02BD02	Treatment and prophylaxis of bleeding in previously treated patients ≥ 12 years of age with haemophilia A (congenital factor VIII deficiency).	NO	> 12 years	
Adalimumab	L04AB04	**Juvenile idiopathic arthritis**: Polyarticular juvenile idiopathic arthritis. Idacio 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 disease-modifying anti-rheumatic drugs (DMARDs). Idacio 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	NO	> 2 years > 4 years > 6 years > 12 years	

Active substance	ATC code	Paediatric indication	Orphan	Paediatric Age	Variations
		section 5.1). Adalimumab has not been studied in patients aged less than 2 years. **Enthesitis-related arthritis**: Idacio 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**: Idacio 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 topicaltherapy and phototherapies. **Hidradenitis suppurativa (HS):** Idacio is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adults and adolescents from 12 years of age with an inadequate response to conventional systemic HS therapy. **Paediatric Crohn's disease**: Idacio 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 Uveitis**: Idacio 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. **Adolescent hidradenitis suppurativa**: Idacio is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adolescents from 12 years of age with an inadequate response to conventional systemic HS therapy.			
Tobramycin	J01GB01	Vantobra is indicated for the management of chronic pulmonary infection due to Pseudomonas aeruginosa in patients aged 6 years and older with cystic fibrosis (CF).	NO	> 6 years	
Glecaprevir / pibrentasvir	J05AP57	Maviret is indicated for the treatment of chronic hepatitis C virus (HCV) infection in adults and in adolescents aged 12 to <18 years	NO	> 12 years	31/01/19 (11/03/19): Extension of indication to extend the Maviret indication to adolescents (from 12 to 18 years of age) with chronic hepatitis C infection, based on new clinical data from study M16-123, an open-label, multi-centre study to evaluate the pharmacokinetics, safety, and efficacy of glecaprevir/pibrentasvir in paediatric subjects with genotypes 1 - 6 chronic hepatitis C virus infection (DORA), using the adult co-formulated tablets in adolescents
Adalimumab	L04AB04	Juvenile idiopathic arthritis: Polyarticular juvenile idiopathic arthritis: Kromeya 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 disease-modifying anti-rheumatic drugs (DMARDs). Kromeya can be given	NO	> 2 years > 4 years > 6 years	

Active substance	ATC code	Paediatric indication	Orphan	Paediatric Age	Variations
		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: Kromeya 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: Kromeya 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. Paediatric Crohn's disease: Kromeya 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 Uveitis: Kromeya 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.			
Miglustat	A16AX06	Yargesa is indicated for the treatment of progressive neurological manifestations in adult patients and paediatric patients with Niemann-Pick type C disease.	NO	> 12 years	
atazanavir	J05AE08	Atazanavir Krka capsules, co-administered with low dose ritonavir, are indicated for the treatment of HIV-1 infected adults and paediatric patients 6 years of age and older in combination with other antiretroviral medicinal products. Based on available virological and clinical data from adult patients, no benefit is expected in patients with strains resistant to multiple protease inhibitors (≥ 4 PI mutations). The choice of Atazanavir Krka in treatment experienced adult and paediatric patients should be based on individual viral resistance testing and the patient's treatment history	NO	> 6 years	
Pegvaliase	A16AB19	Palynziq is indicated for the treatment of patients with phenylketonuria (PKU) aged 16 years and older who have inadequate blood phenylalanine control (blood phenylalanine levels greater than 600 micromol/l) despite prior management with available treatment options.	YES	> 16 years	
Autologous CD34+ cells encoding βA-T87Q-globin gene	B06A	Zynteglo is indicated for the treatment of patients 12 years and older with transfusion-dependent β-thalassaemia (TDT) who do not have a β0 /β0 genotype, for whom haematopoietic stem cell (HSC) transplantation is appropriate but a human leukocyte antigen (HLA)-matched related HSC donor is not available	YES	> 12 years	
Miglustat	A16AX06	Miglustat Gen.Orph is indicated for the treatment of progressive neurological manifestations in adult patients and paediatric patients with Niemann-Pick type C disease	NO	> 12 years	
Zanamivir	J05AH01	Dectova is indicated for the treatment of complicated and potentially life-threatening influenza A or B virus infection in adult and paediatric patients (aged ≥6 months) when:	NO	> 6 months	

Active substance	ATC code	Paediatric indication	Orphan	Paediatric Age	Variations
		- The patient's influenza virus is known or suspected to be resistant to anti-influenza medicinal products other than zanamivir, and/or - Other anti-viral medicinal products for treatment of influenza, including inhaled zanamivir, are not suitable for the individual patient.			
Turoctocog alfa pegol	B02BD02	Treatment and prophylaxis of bleeding in patients 12 years and above with haemophilia A (congenital factor VIII deficiency).	NO	> 12 years	
Dupilumab	D11AH05	Atopic Dermatitis: Dupixent is indicated for the treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy. Asthma: Dupixent is indicated in adults and adolescents 12 years and older as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO (see section 5.1), who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment.	NO	> 12 years	
Hydroxycarbamide	L01XX05	Xromi is indicated for the prevention of vaso-occlusive complications of Sickle Cell Disease in patients over 2 years of age	NO	> 2 years	
emtricitabine / tenofovir disoproxil	J05AR03	Treatment of HIV-1 infection: Emtricitabine/Tenofovir disoproxil Mylan is also indicated for the treatment of HIV-1 infected adolescents, with NRTI resistance or toxicities precluding the use of first line agents. Pre-exposure prophylaxis (PrEP): Emtricitabine/Tenofovir disoproxil Mylan is indicated in combination with safer sex practices for preexposure prophylaxis to reduce the risk of sexually acquired HIV-1 infection in adults and adolescents at high risk.	NO	> 12 years weighing at least 35 kg	
Treosulfan	L01AB02	Treosulfan in combination with fludarabine is indicated as part of conditioning treatment prior to allogeneic haematopoietic stem cell transplantation (alloHSCT) in adult patients with malignant and non-malignant diseases, and in paediatric patients older than one month with malignant diseases.	NO	> 1 month	
Trientine dihydrochloride	A16A	Cufence is indicated for the treatment of Wilson's disease in patients intolerant to D-Penicillamine therapy, in adults, adolescents and children aged 5 years or older.	NO	> 5 years	
Insulin aspart	A10AB05	Treatment of diabetes mellitus in adults, adolescents and children aged 1 year and above.	NO	> 1 year	27/06/19 (31/07/19): Extension of Indication to include treatment of children and adolescents aged 1 year and above based on data from the phase 3b clinical trial NN1218-4101, supported by data from the Clinical Pharmacology trials NN1218-4371 and clinical study NN1218-3888 which was included in the initial MAA
Plerixafor	L03AX16	***Paediatric patients (1 to less than 18 years)***: Mozobil is indicated in combination with G-CSF to enhance mobilisation of haematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in children with lymphoma or solid malignant tumours, either: - pre-emptively, when circulating stem cell count on the predicted day of collection after adequate mobilization with G-CSF (with or without	YES	> 1 year	28/03/19 (02/09/2019): Extension of Indication to include paediatric patients aged 1 to 18 years for Mozobil; as a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated

Active substance	ATC code	Paediatric indication	Orphan	Paediatric Age	Variations
		chemotherapy) is expected to be insufficient with regards to desired hematopoietic stem cells yield, or - who previously failed to collect sufficient haematopoietic stem cells			
Dolutegravir sodium Lamivudine	J05R	Dovato is indicated for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults and adolescents above 12 years of age weighing at least 40 kg, with no known or suspected resistance to the integrase inhibitor class, or lamivudine	NO	> 12 years weighing at least 40 kg	
Lacosamide	N03AX18	Lacosamide UCB is indicated as monotherapy and adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in adults, adolescents and children from 4 years of age with epilepsy.	NO	> 4 years	
Ranibizumab	S01LA04	Lucentis is indicated in preterm infants for: • The treatment of retinopathy of prematurity (ROP) with zone I (stage 1+, 2+, 3 or 3+), zone II (stage 3+) or AP-ROP (aggressive posterior ROP) disease.	NO	Preterm	25/07/19 (03/09/19): Extension of Indication to include: A new indication for Lucentis vial presentation: treatment of retinopathy of prematurity (ROP) in preterm infants
Cannabidiol	N03AX	Epidyolex is indicated for use as adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS), in conjunction with clobazam, for patients 2 years of age and older.	YES	> 2 years	
Deferasirox	V03AC03	Deferasirox Mylan is indicated for the treatment of chronic iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) in patients with beta thalassaemia major aged 6 years and older. Deferasirox Mylan is also indicated for the treatment of chronic iron overload due to blood transfusions when deferoxamine therapy is contraindicated or inadequate in the following patient groups: – in paediatric patients with beta thalassaemia major with iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) aged 2 to 5 years, – in adult and paediatric patients with beta thalassaemia major with iron overload due to infrequent blood transfusions (<7 ml/kg/month of packed red blood cells) aged 2 years and older, – in adult and paediatric patients with other anaemias aged 2 years and older. Deferasirox Mylan is also indicated for the treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with non-transfusiondependent thalassaemia syndromes aged 10 years and older.	NO	> 2 years	
Liraglutide	A10BJ02	Victoza is indicated for the treatment of adults, adolescents and children aged 10 years and above with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise • as monotherapy when metformin is considered inappropriate due to intolerance or contraindications • in addition to other medicinal products for the treatment of diabetes. For study results with respect to combinations, effects on glycaemic control and cardiovascular events, and the populations studied.	NO	> 10 years	27/06/19 (09/08/19): Extension of Indication to include treatment of children and adolescents aged 10 years and above with type 2 diabetes mellitus based on Study NN2211-1800;
Larotrectinib	L01XE53	VITRAKVI as monotherapy is indicated for the treatment of adult and paediatric patients with solid tumours that display a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion, - who have a disease that is locally advanced, metastatic or where surgical resection is likely to	NO	> 1 month	

Active substance	ATC code	Paediatric indication	Orphan	Paediatric Age	Variations
		result in severe morbidity, and - who have no satisfactory treatment options			
Belimumab	L04AA26	Benlysta is indicated as add-on therapy in patients aged 5 years and older with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g., positive anti-dsDNA and low complement) despite standard therapy	NO	> 5 years	19/09/19 (21/10/19): Extension of indication to include patients aged 5 years and older in the current approved indication for Benlysta (belimumab powder for solution for infusion 120 mg/ml and 400 mg/ml)

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.