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Brief report

[Translated article] Current situation and evolution of the availability of drugs in the pediatric population in Spain

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ABSTRACT

Objective: To analyze the characteristics of the new medicines approved in the pediatric population in the last 3 years, both those with studies only in the pediatric population and those that extend their indication in this population group, as well as the current situation in relation to their marketing and financing.
Methods: Descriptive observational study of all drugs that include an indication in the pediatric population in Spain (by extension of the indications of drugs already authorized or because they are new drugs that already include an indication in this population group), from January 2019 to March 2022.
Results: During the study period, 129 drugs included their indication in the pediatric population. 13.9% of them are not marketed, 46.5% are in a situation of non-financing, under study or without a request for financing, and 4.6% are financed for a specific pediatric subpopulation. 52.7% are original drugs, 4.7% are generic, 38.8% are biological, 3.8% are biosimilar, and 17.8% are orphan drugs. 57.36% of these medicines obtain the pediatric indication due to extension of the indication and 42.64% obtain it because they are new medicines that already include their studies in the pediatric population.
Conclusions: Drugs with authorized indications are increasingly available in the pediatric population and the trend is to extend the indication of authorized drugs to the adult population. However, barriers in terms of financing and marketing need to be expedite and overcome to facilitate access to them.

Situación actual y evolución de la disponibilidad de medicamentos en la población pediátrica en España

Palabras clave:
Ensayos clínicos
Uso no autorizado en ficha técnica
Aprobación de medicamentos
Utilización de medicamentos

RESUMEN

Objetivo: Analizar las características de los nuevos medicamentos aprobados en población pediátrica en los últimos tres años, tanto de aquellos medicamentos con estudios únicamente en población pediátrica, como de aquellos que amplían su indicación en este grupo de población, así como la situación actual en relación a su comercialización y financiación.
Métodos: Estudio observacional descriptivo de todos los medicamentos que incluyen indicación en población pediátrica en España (por extensión de las indicaciones de medicamentos ya autorizados o por ser nuevos medicamentos que ya incluyen indicación en este grupo de población), desde enero de 2019 hasta marzo de 2022.
Resultados: En el periodo de estudio 129 medicamentos incluyeron su indicación en población pediátrica. A pesar de esto, el 13,9% de ellos, no están comercializados, el 46,5% se encuentran en situación de no financiación, en estudio o sin petición de financiación y el 4,6% están financiados para una determinada subpoblación pediátrica. El 52,7% son medicamentos originales, el 4,7% son genéricos, el 38,8% son biológicos, el 3,8% son biosimilares y el 17,8% son medicamentos huérfanos. El 57,36% de estos medicamentos obtienen la indicación pediátrica por extensión de la indicación y el 42,64% la obtienen por ser nuevos medicamentos que ya incluyen sus estudios en población pediátrica.
Conclusiones: La población pediátrica dispone cada vez más de medicamentos con indicación autorizada siendo la tendencia a extender la indicación de medicamentos autorizados en población adulta. No obstante, es preciso

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agilizar y superar las barreras en lo que se refiere a financiación y comercialización para facilitar el acceso a los mismos.

Introduction

Regulation (EC) 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for pediatric use entered into term in 2007. Before that date, research on and authorization of new medicinal products for use in the pediatric population were not adequately regulated by any law. This Regulation guarantees the efficacy and safety of new approved medicinal products for use in the pediatric population. In this sense, the creation of the European Medicines Agency's (EMA) Paediatric Committee in 2007 was a landmark in this field of medicine. The aim of this committee is to provide objective scientific evidence and assess pediatric investigation plans and the development of medicines for children.[1]

In 2017, the European Commission released an evaluation of the level of implementation of Regulation 1901/2006 in the European Union. The results showed an increase in the volume of authorizations of medicinal products for pediatric patients during the study period. However, the evaluation also demonstrated the need for promoting the development of new medicinal products for diseases that solely affect the pediatric population, which have differences and particularities with respect to the adult population.[2]

Research on medicinal products in the pediatric population is extremely complex. Firstly, research in children raises ethical concerns associated with the vulnerability of the study population. In addition, there may be scant interest due to limited economic profit. Other challenges to the development of pediatric clinical trials include variability in the pediatric population with respect to adults, with significant differences in pharmacokinetics, pharmacodynamics, and adverse reactions. Other factors include changes in the samples resulting from growing and maturing processes and their specific diseases.[3,4]

In 2017, a national network of pediatric clinical trials (RECLIP) was created in Spain. RECLIP provides support, experience, and infrastructure to optimize the development of pediatric clinical trials. The purpose is to ensure that the pediatric population benefits from new medicinal products, which efficacy, safety, and dosing have been previously evaluated and validated using standardized methods.

The adaptation of adult treatments for use in the pediatric population entails a variety of challenges. Firstly, dosing is complex due to the lack of availability of pediatric drug formulations. This situation may lead to dosing errors and inadequate drug administration, which may compromise patient safety and cause severe adverse reactions.[5]

Secondly, according to EMA's 2004 Report, less than 50% of pediatric formulations have been tested in the pediatric population. As a result, these formulations are often prescribed off-label or in conditions different to those indicated in the label. This occurs in 90% of neonatal units, 45% of pediatric hospitalization units, and 10%–20% in primary care.[6]

According to another EMA evaluation report, a study conducted in a pediatric hospital revealed that 95% of adverse drug reactions were associated with off-label use of prescription drugs, as compared to 3.9% of adverse reactions associated with on-label use.[7]

In light of the aforementioned evidence, a broader therapeutic armamentarium is required for the pediatric population. For such purpose, the safety and efficacy of pediatric formulations should be correctly assessed and approved by the relevant regulatory authorities. This will guarantee a correct use of drugs and help overcome the limitations described above.

The growing demand for safe, effective drugs in pediatric hospitals in Spain makes it necessary to better understand the characteristics and state of affairs of newly authorized pediatric drugs in our country. The results of this study will ensure a safe, more effective use of pediatric drugs. This study provides a summary of newly approved pediatric medicines, which can be used as an easy-to-use consultation tool.

The aim of this study was to analyze newly approved drugs for pediatric indications and provide a picture of the state of affairs regarding the marketing and funding of these products.

Methods

A descriptive, observational study of all drugs labeled with pediatric indications approved between January 2019 and March 2022. An analysis was performed of the characteristics of recently approved drugs tested either in clinical trials solely performed in children, or which indication has been extended to this population.

As a source of information, we used the monthly newsletter of the Spanish Agency for Medicines and Medical Devices (AEM). This newsletter provides information in relation to changes in the indications of approved medicines and newly approved drugs. We collected and analyzed data on indications for pediatric use. At the end of the study period (March 2022), information about the funding status of drugs was retrieved from BIFIMED, the Spanish Ministry of Health's medicine finder engine that shows the pricing and reimbursement (P&R) status of medicinal products.

Results

The medicinal products identified were related to the fields of infectious diseases (30%); oncohematology (10.83%); pulmonology (10%); neurology (9.16%); endocrinology (6.66%); dermatology (5.83%); metabolics-genetics (5%); rheumatology (4.16%); internal medicine (4.16%); nephrology (3.33%); ophthalmology (2.5%); gastroenterology (2.5%); allergology; (2.5%); psychiatry (1.6%), and cardiology (1.6%).

During the study period, 129 new medicines were labeled with a pediatric indication; 13.9% ($n=18$) are not currently marketed, 46.5% ($n=60$) have not been approved for P&R, are still being tested or P&R has not been requested; 4.6% ($n=6$) have been approved for P&R for a specific subpopulation of pediatric patients, but not for all labeled pediatric indications. By type of medicine, 52.7% ($n=68$) were original; 4.7% ($n=6$) were generic drugs; 38.8% ($n=50$) were biologicals; 3.8% ($n=5$) were biosimilar drugs, and 17.8% ($n=23$) were orphan drugs.

In 57.36% ($n=74$) of medicines, the pediatric indication was approved by extension of the indication for the adult population. In contrast, 42.64% ($n=55$) were new medicinal products that had been tested in the pediatric population. Table 1 summarizes new medicinal products labeled with a pediatric indication or approved for use in pediatrics by extension.

Comparison of data for our study period against the 3 previous years in our country reveals that, in 2016, a total of 34 drugs were approved for use in the pediatric population (13 new drugs and 21 by extension of the indication). In 2017, there was a 14.7% increase in the number of these types of drugs (18 new drugs and 21 by extension). In 2018, a 32.4% increase was observed with respect to 2016, including 23 new drugs and 22 by extension of its indication. Between 2019 and early 2022, 129 drugs were approved for use in the pediatric population (74 new drugs and 55 by extension of the indication).

Table 1
Newly approved medicines for use in pediatrics and medications labeled with indication for the pediatric population by extension.

New medicinal products labeled with a pediatric indication		
Drug (pharmaceutical formulation)	New indications	Marketed/reimbursed
Abatacept (Orenciace:sup]®)	AIJP with MTX, ≥6 years, insufficient response/intolerance FAME and >1 anti-TNF	Yes/Yes
Adalimumab (Amsparity®)	Insufficient response/intolerance to DMT. Active PJIA ≥2 years; enthesitis-related arthritis ≥6 years; severe plaque psoriasis ≥4 years; moderate–severe hidradenitis suppurativa ≥12 years; CD ≥6 years; non-infectious uveitis ≥2 years	No/No
Adalimumab (Hukyndra®)	Insufficient response/intolerance to DMT. Active PJIA ≥2 years; enthesitis-related arthritis ≥6 years; severe plaque psoriasis ≥4 years; moderate–severe hidradenitis suppurativa ≥12 years; CD ≥6 years; non-infectious uveitis ≥2 years	Yes/Yes
Artesunate (Amivas®)	Severe malaria, first-line treatment	No/No
Avalglucosidase alfa (Nexviadyme®)	Enzyme replacement medicine, Pompe disease	No/No
Baloxavir Marboxil (Xofluza®)	Treatment of non-complicated influenza and post-exposure prophylaxis ≥12 years	No/No
Berotralstat (Orladeyo®)	Prevention of recurrent hereditary angioedema in >2 years	No/No
Cannabidiol (Epidiolex®)	Convulsions secondary to Lennox–Gastaut or Dravet disease, in associated with clobazam >2 years	Yes/Yes
Casirivimab/Imdevimab (Ronapreve®)	Prophylaxis and treatment of COVID-19 ≥12 years and ≥40 kg, without oxygen therapy and higher risk for severe disease progression	Yes/under study or P&R not requested
Autologous CD34 cells + vectors encoding the BA-T87Q-GLOBINA 1,2–20 gene + 106 cells/ml dispersion for infusion (Zynteglo®)	≥12 years with non-β0/β0 transfusion-dependent beta-thalassemia	No/No
Potassium citrate/Potassium hydrogen carbonate (Sibnayal®)	Renal tubular acidosis >1 years	No/No
Methylthioninium chloride (Proveblue)	Acute drug/chemically induced methemoglobinemia, 0–17 years	Yes/Yes
Crisaborole (Staquis®)	Mild–moderate atopic dermatitis and ≤40% involvement, ≥2 years	No/No
Crizanlizumab (Adakveo®)	Prevention of recurrent vasooclussive crises, ≥16 years with sickle cell disease	Yes/under study or P&R not requested
Autogenous CD34 + cell culture enriched in hematopoietic stem cells and progenitor cells transduced *ex vivo* using a lentiviral vector encoding human Arylsulfatase A gene. (Libmeldy®)	MLD in children with late childhood or early juvenile forms, without clinical manifestations of the disease; in children with early juvenile form, with early clinical manifestations of the disease who can still work without aid and before onset of cognitive deterioration.	Yes/under study or P&R not requested
Trientine dihydrochloride (Cufence®)	Wilson disease >5 years intolerance to D-penicillamine	Yes/Yes
Dolutegravir/Lamivudine (Dovato®) 50 mg/300 mg	HIV-1 >12 years, ≥40 kg, without resistance to integrase inhibitors or 3TC	Yes/Yes
Elexacaftor Tezacafyor/Ivacaftor (Kaftrio®)	In combination with ivacaftor for CF in ≥12 years, with the F508del mutation and minimal function F508del mutation	Yes/Yes
Entrectinib (Rozlytrek®)	Monotherapy; ≥12 years with solid tumors expressing the INTRK that are locally advanced or metastatic or without therapeutic options	Yes/P&R not approved
Etanercept (Nepexto®)	JIA in >2 years; psoriatic arthritis and arthritis with enthesitis in >12 years; severe plaque psoriasis in >6 years	No/No
Fenfluramine (Fintepla®)	In combination, in convulsions associated with Dravet syndrome; ≥2 years	Yes/under study or P&R not requested
Givosiran (Givlaari®)	Acute hepatic porphyria; ≥12 years	Yes/No
Nasal glucagon (Baqsimi®)	Severe hypoglycemia, ≥4 years with DM	Yes/Yes
Glucarpidase (Voraxaze®)	To reduce toxic plasma MTX concentrations in ≥28 days, with reduced clearance or risk of toxicity	Yes/yes (foreign medicinal products)
Oral delayed-release hydrocortisone (Plenadren®)	Congenital adrenal hyperplasia >12 years	Yes/P&R not approved
Hydroxycarbamide (Xromi®)	Prevention of vaso-occlusive complications of sickle cell disease; ≥2 years	No/No
Non-specific human immunoglobulin (Hizentra®)	PID replacement therapy	Yes/Yes
Imatinib (Koanaa®)	Newly diagnosed Ph + CML in non-candidate to HPSCT; in Ph + CML in chronic stage after failure of treatment with interferon alfa, or in accelerated phase or blast crisis, and in newly diagnosed Ph + ALL, integrated with CT	No/No
Indacaterol/Mometasone furoate (Atectura Breezhaler®/ Bemrist Breezhaler®):	Maintenance therapy for asthma; ≥12 years, not controlled with conventional therapies	Yes/Yes
Guanfacine (Intuniv®)	Adjuvant therapy in ADHD	Yes/Yes
Larotrectinib (Vitrakvi®)	In solid tumors with neurotrophic receptor tyrosine kinase (NTRK) gene fusions in locally advanced/metastatic cancer or surgical resection associated with high mortality rates and when it is the only therapeutic option available	Yes/P&R not approved
Lonapegsomatropin (Lonapegsomatropin Ascendis Pharma®)	Growth disorder for growth hormone hyposecretion ≥3 years	No/No
Lumasiran (Oxlumo®)	Type I hyperoxaluria	Yes/under study or P&R not requested
Melfalán (Phelinum®)	At high doses in MM, malignant lymphomas, ALL and AML, childhood neuroblastoma, ovarian cancer, and breast adenocarcinoma	No/No
Obiltoxaximab (Obiltoxaximab SFL®)	Treatment, in combination with pulmonary carbuncle by *Bacillus anthracis* post-exposure prophylaxis when alternative therapies are not appropriate or are not available	No/No
Onasemnogene Abeparvovec (Zolgensma®)	AME 5q with a biallelic mutation in the SMN1 gene and a clinical diagnosis of type 1 SMA, or SMA 5q with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene	Yes/Yes
Cholic acid (Orphacol®)	3β-hydroxy-Δ5-C27-steroid dehydrogenase or Δ4–3-Oxosteroid-5β-reductase deficiency in ≥1 month	Yes/Yes
Sodium oxybate (Xyrem®)	Narcolepsy with cataplexy, ≥7 years	Yes/Yes
Injectable pegvaliase (Palynziq®)	≥16 years with phenylketonuria with inadequate phenylalanine control	Yes/P&R not approved

Table 1 (*continued*)

New medicinal products labeled with a pediatric indication		
Drug (pharmaceutical formulation)	New indications	Marketed/reimbursed
Plerixafor (Mozobil®)	1–18 years, in combination with G-CSF, to boost hematopoietic stem cell mobilization in PB for aHSCT in lymphoma or malignant solid tumors; or in some circumstances involving collected cell count	Yes/Yes
Defatted powder of peanuts- *Arachis hypogaea* L, (Palforzia®)	4–17 years; allergy to peanuts	No/No
Remdesivir (Veklury®)	COVID-19+; ≥12 years; ≥40 kg, with pneumonia, and oxygen therapy	Yes/Yes
Risdiplam (Evrysdi®)	5q SMA in >2 months with a clinical diagnosis of type 1, 2 or 3 SMA, or with 1–4 copies of the SMN2 gene	Yes/under study or P&R not requested
Ruxolitinib (Jakavi®)	Acute/chronic GvHD in ≥12 years, with inadequate response to steroids or other systemic diseases	Yes/No
Somatrogon (Ngenla®)	Growth disorder in progression 3 years secondary to growth hormone hyposecretion	Yes/under study or P&R not requested
Sotrovimab (Xevudy®)	COVID-19 ≥12 years and ≥40 kg, without oxygen therapy and higher risk for severe disease progression	Yes/under study or P&R not requested
Tecovirimat (Tecovirimat Siga®)	Smallpox, monkeypox and bovine pox, ≥13 kg and in complications due to *vacinnia* virus replication following vaccination	No/No
Tixagevimab/Cilgavimab (Evusheld®)	COVID-19 pre-exposure prophylaxis + ≥12 years; 40 kg	Yes/under study or P&R not requested
Turoctocog alfa pegol (Esperoct®)	Treatment and prophylaxis of hemorrhage in ≥12 years, with A hemophilia	Yes/Yes
Conjugated vaccine of meningococcal groups A,C,W and Y (MenQuadfi®)	Active immunization ≥12 months against invasive meningococcal disease by serogroups A, C, W and Y de *Neisseria meningitidis*	Yes/Yes
Vaccination against Ebola: Trivalent, recombinant, non-replicating MVA-BN-FILO (Mvabea®) and vaccination against Ebola: Monovalent recombinant unable to replicate with the AD26 vector that encodes the full-length glycoprotein (GP) of the Zaire Ebolavirus (Zabdeno®)	In combination, in active immunization for the prevention of Ebola virus in ≥1 year	Yes/under study or P&R not requested
Living, oral vaccine for recombinant cholera (Vaxchora®)	Active immunization against disease by the *cholerae* vibrio, O1 serogroup, in ≥6 years	Yes/Yes
Voxelotor (Oxbryta®)	In monotherapy/combination with hydroxycarbamide in hemolytic anemia for sickle cell disease; ≥12 years	No/No
Zanamivir (Dectova®)	≥6 months; complicated influenza A virus and life-threatening when Zanamivir is not an option	Yes/P&R not approved
Medicinal products with extended indication to pediatrics		
Drug (pharmaceutical formulation)	New indications	Marketed/reimbursed
Glecaprevir/Pibrentasvir (Marivet®)	HCV+; 12–17 years	Yes/Yes
Tenofovir disoproxil (Viread®)	HBV of 6–12 years with active compensated liver disease	Yes/Yes
Liraglutid (Victoza®)	>10 years and in DM2 poorly controlled with diet and physical exercise, metformin is not appropriate, in monotherapy/combination	Yes/Yes
Ceftaroline (Zinforo®)	IPPBc and CAP	Yes/yes for SSTIs, not for CAP
Dupilumab (Dupixent®)	Moderate–severe atopic dermatitis, >12 years	Yes/Yes
Non-specific intravenous immunoglobulin (Flebogamma®)	2–18 years with IDP with lack of antibody production; SID in severe recurrent infection, ineffective or proven failed treatment at PSAF or IgG <4 g/l; Kawasaki disease concomitant to AAS; CID polyneuropathy; MM neuropathy	Yes/Yes
Ranibizumab (Lucentis®)	Retinopathy of prematurity with zone I (stage 1 +, 2 +, 3 o 3 +), zone II (estadio 3 +) or aggressive progressive ROP	Yes/Yes
Belimumab (Benlysta®)	>5 years in active SEL, positive antibodies and high level of disease activity despite standard treatment	Yes/Yes
Ivacaftor Granules (kalydeco®)	In ≥6 months and ≥25 kg with CF with class III mutation in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R	Yes/No. CF ≥2 years and <25 kg and all those mutations
Fidaxomicin (Dificlir®)	Infection by *C. difficile* ≥12.5 kg. Oral granules in <18 years	Yes/Yes
Bedaquiline (Sirturo®)	MDR-TB, in combination, 12–18 years and ≥30 kg	Yes/P&R not approved
Ustekinumab (Stelara®)	Moderate–severe plaque psoriasis ≥6 years	Yes/Yes
Rituximab	Combined with CTX in ≥6 months, with DLBCL, Burkitt lymphoma, mature B cell ALL or in naive patients with advanced-stage Burkitt lymphoma Combined with glucocorticoids remission induction ≥2 years, with granulomatosis with polyangiitis (Wegener) and with microscopic, active and severe polyangiitis	Yes/Yes
Darunavir/Cobicistat (Rezolsta®)	HIV: ≥12 years and ≥40 kg	Yes/Yes
Cobicistat (Tybost®)	HIV: as a pharmacokinetic enhancer of atazanavir or darunavir, ≥12 years, with restrictions	Yes/Yes
Etravirina (Intellence®)	HIV-1: pretreated ≥2 years	Yes/Yes
Conestat alfa (Ruconest®)	Acute angioedema, ≥2 years	Yes/Yes
Caplacizumab (Cablivi®)	In >12 years and ≥40 kg, with aTTP, concurrent with plasma exchange and immunosuppression	Yes/Yes
Anidulafungin (Ecalta®)	Invasive candidiasis, ≥1 month	Yes/Yes
Ledispavir/Sofosbuvir (Harvoni®)	HCV+, ≥years	Yes/No
Sofosbuvir (Sovaldi®)	HCV, ≥3 years, in combination	Yes/No
Ivacaftor (kalydeco®)	CF and R117H CFTR mutation	Yes/No
Tedizolid (Sivextro®)	IPPB ≥12 years	Yes/Yes

(*continued on next page*)

Table 1 (*continued*)

Medicinal products with extended indication to pediatrics		
Drug (pharmaceutical formulation)	New indications	Marketed/reimbursed
Ixekizumab (Taltz®)	Moderate–severe plaque psoriasis, ≥6 years and ≥25 kg, candidates for systemic treatment	Yes/Yes
Secukinumab (Cosentyx®)	Moderate–severe plaque psoriasis, ≥6 years, candidates for systemic treatment	Yes/Yes
Sofosbuvir/Velpatasvir (Epclusa®)	HCV, ≥ 6 years and ≥17 kg	Yes/Yes
Burosumab (Crysvita®)	X-linked hypophosphatemia, with signs of bone disease, 1–17 years	Yes/Yes
Human immunoglobulin (HyQvia®)	SID with recurrent severe infections, ineffective antimicrobial treatment and non-specific antibody failure (failure to achieve a ≥2-fold increase in IgG antibody titer against pneumococcal polysaccharides and polypeptide antigenic vaccines) or serum IgG concentration <4 g/l	Yes/Yes
Ivacaftor (Kalydeco®)	CF, in monotherapy, >6 years or >25 kg and one of the following CFTR gene mutations: R117H, G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N o S549R. In combination with Ivacaftor/Tezacaftor/Elexacaftor, in CF in ≥12 years with the F508del mutation and minimal function CFTR mutation.	Yes/Yes
Lurasidone (Latuda®)	Schizophrenia, ≥13 years	Yes/Yes
Catridecacog (Novothirteen®)	Episodes of bleeding during routine prophylaxis in all groups	Yes/P&R not approved
Darunavir (Prezista®)	Co-administered with Cobicistat in HIV, ≥12 years and ≥40 kg	Yes/Yes
Delamanid (Deltyba®)	MDR-TB, in combination, ≥30 kg, when other treatment is not possible due to resistance or non-tolerability	Yes/Yes
Perampanel (Fycompa®)	Concomitant treatment in partial onset crises in ≥4 years and primary generalized tonic–clonic seizures in ≥7 years with generalized idiopathic epilepsy	Yes/Yes
Quadrivalent influenza vaccine (Flucelvax Tetra®)	Prophylaxis of influenza, ≥2 years	Yes/P&R not approved
Ivacaftor Granules (kalydeco®)	≥4 months and ≥25 kg with CF and one of the following CFTR gene mutations: R117H, G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N o S549R. In combination with Ivacaftor/Tezacaftor/Elexacaftor, in CF in >6 years with the F508del mutation and minimal function mutation in the CFTR gene	Yes/No
Sucroferric oxyhydroxide (Velphoro®)	Serum phosphorus control, ≥2 years with CKD in stage 4–5 or on dialysis	Yes/Yes
Ceftazidime-avibactam (Zavicefta®)	>3 months, in complicated IAI and UTI, including pyelonephritis, HAP, including VAP	Yes/No
Dupilumab (Dupixent®)	Severe atopic dermatitis, 6–11 years, in candidates for systemic treatment	Yes/Yes
Adalimumab (Humira®)	Moderate–severe UC, ≥6 years, and contraindication/inadequate response to conventional treatment	Yes/Yes
Lacosamide (Vimpat®)	Primary generalized tonic–clonic crises in ≥4 years	Yes/Yes
Dabigatran (Pradaxa®)	VT and prevention of recurrent thromboembolism in <18 years	Yes/No
Dolutegravir (Tivicay®)	HIV, >4 weeks, >3 kg	Yes/No, ≥6 years
Rivaroxabán (Xarelto®)	VT and prevention of recurrent thromboembolic events in full-term neonates, and <18 years, after initial treatment of ≥5 days with parenteral anticoagulants	Yes/No
Bedaquiline (Sirturo®)	MDR-TB, in combination, >5 years and ≥15 kg for resistance/intolerance to first-choice treatment	Yes/P&R not approved
Pembrolizumab (Keytruda®)	In ≥3 years, with relapsed or refractory HL, who have not responded to TAHP, after ≥2 years when aHSCT is not a treatment option	Yes/No
Cannabidiol (Epydiolex®)	>2 years, convulsions associated with tuberous sclerosis	Yes/No
Ivacaftor (Kalydeco®) and Ivacaftor/Tezacaftor (Symkevi®)	>12 years with CF with ≥1CFTR mutation in the F508 gene	Yes/Yes
Liraglutide (Saxenda®)	>12 years, in weight control, in combination with a low-calorie diet and physical activity, meeting BMI criteria	Yes/P&R not approved
Adalimumab (Humira®)	Combined with MTX in active JIA, 4–17 years and insufficient response ≥1 DMARD or monotherapy when treatment with MTX is not possible	Yes/Yes
Nitric oxide (INOmax®)	Concurrently with assisted ventilation and other adequate agents in PAH peri- and post-cardiac surgery, 0–17 years	Yes/Yes
Sildenafil (Revatio®)	Primary PAH or associated with congenital cardiac disease, 1–17 years	Yes/Yes
Delamanid (Deltyba®)	MDR-TB, in combination, >10 years for resistance/intolerance to first-choice treatment	Yes/Yes
Ravulizumab (Ultomiris®)	≥10 kg with PNH on hemodialysis with active or stable disease after treatment with eculizumab ≥6 months	Yes/Yes
Ambrisentan (Volibris®)	OMS functional class II-III PAH, 8–18 years	Yes/Yes
Sofosbuvir/Velpatasvir/Voxilaprevir (Vosevi®)	HCV +; ≥12 years, ≥30 kg	Yes/No
Mepolizumab (Nucala®)	Relapsing–remitting or refractory eosinophilic granulomatosis with polyangiitis ≥6 years	Yes/No
Elbasvir/Grazoprevir monohydrate (Zepatier®)	HCV +; ≥12 years, >30 kg	Yes/Yes
Dapagliflozin (Edistride/Forxiga®)	Poorly controlled DM2, >10 years in combination with diet and physical exercise	Yes/No
Nonspecific human immunoglobulin (Hizentra®)	Replacement therapy in SID with severe infections, ineffective antibiotic treatment and specific antibody failure, or serum level of IgG < 4 g/l	Yes/No
Evolocumab (Repatha®)	>10 years with homo/heterozygous familial hypercholesterolemia	Yes/No
Dengue tetravalent vaccine (Dengvaxia®)	Dengue prophylaxis for serotypes 1,2,3, and 4; ≥6 years, with previous confirmed infection	No/No
Sofosbuvir/Velpatasvir (Epclusa®)	HCV; 3 years	Yes/No
Tezacaftor/Ivacaftor/Elexacaftor (Kaftrio®)	In combination with ivacaftor in CF in ≥6 years, with ≥1 F508del mutation in the CFTR gene	Yes/No
Ivacaftor (Kalydeco®)	In combination with Ivacaftor/Tezacaftor/Elexacaftor, in CF in ≥6 years,	Yes/No

Table 1 (*continued*)

Medicinal products with extended indication to pediatrics		
Drug (pharmaceutical formulation)	New indications	Marketed/reimbursed
	with the F508del mutation and minimal function CFTR mutation.	
Posaconazol (Noxafil®)	≥2 years; aspergillosis, fusariosis, chromoblastomycosis, and coccidiodomycosis, refractory or intolerant to first-choice antifungals. Patients receiving remission induction CTX for AML or MDS or TPH receptors with immunosuppressive therapy with a high risk for developing IFI	Yes/Yes
Brivaracetam (Briviact®)	Concomitant therapy in partial onset seizures, ≥2 years	Yes/No. ≥ 4 years Yes
Duplilumab (Dupixent®)	6–11 years with severe asthma and eosinophilia and/or high level of fractional exhaled FeNO not controlled with inhaled corticosteroids	Yes/No. ≥12 years Yes
Lacosamida (Lacosamida UCB®, Vimpat®)	>2 years in monotherapy for partial-onset epileptic seizures	Yes/No. ≥4 years Yes
Dimethyl fumarate (Tecfidera®)	Relapsing–remitting MS, ≥13 years	Yes/Yes
Doravirine/Lamivudine/Tenofovir disoproxil fumarate (Delstrigo®)	≥12 years and ≥ 35 kg, HIV-1 +, non-resistance to NNTRI, 3TC, or TDF, and toxicity precluding use of other non-TDF-containing regimens	Yes/P&R not approved
Doravirine (Pifeltro®)	ART in combination, ≥12 years and ≥35 kg, HIV-1 +, without resistance to NNRTI	Yes/Yes
COVID-19 mRNA vaccine nucleoside modified (Spikevax®)	COVID-19 prophylaxis, ≥6 years	Yes/under study or P&R not requested
Ruxolitinib (Jakavi®)	GvHD ≥12 years, with inadequate response to steroids or other systemic diseases	Yes/No

JIA: Juvenile Idiopathic Arthritis; PJIA: Poliarticular Juvenile Idiopathic Arthritis; SMA: Spinal Muscular Atrophy; ASA: Acetylsalicylic Acid; UC: Ulcerative Colitis; DM: Diabetes Mellitus; CD: Crohn's Disease; GvHD: Graft-Versus-Host Disease; MS: Multiple Sclerosis; CKD: Chronic Kidney Disease; FeNO: Nitric Oxide; CF: Cystic Fibrosis; G-CSF: Franulocyte-Colony Stimulating Factor; PAH: Pulmonary Arterial Hypertension; PNH: Paroxysmal Nocturnal Hemoglobinuria; PID: Primary Immunodeficiency; SID: Secondary Immunodeficiency; IFI: Invasive Fungal Invasion; IAI: Intraabdominal Infection; SSTIs: Skin and Soft-Tissue Infections; UTI: Urinary Tract Infection; DLBCL: Diffuse Large B Cell Lymphoma; Metachromatic Leukodystrophy; SEL Systemic Lupus Erythematosus; HL Hodgkin lymphoma; ALL: Acute Lymphoid Leukemia; AML: Acute Myeloid Leukemia; CML: Chronic Myeloid Leukemia; MDR-TB: Multi drug resistant Tuberculosis; MM: Multiple Myeloma; MTX: methotrexate; CAP: Community Associated Pneumonia; HAP: Hospital Acquired Pneumonia; NNRTI: Non-nucleoside reverse transcriptase inhibitors; Attp: Acquired Thrombocytopenic Purpura; CTX: chemotherapy; ROP: Retinopathy of Prematurity; MDS: Myelodysplastic syndrome; PB Peripheral Blood; aHSCT Autogenous Hematopoietic Stem Transplantation; ART: Antiretroviral treatment; ADHD: Attention deficit disorder; VT: venous thrombosis; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus; MV: Mechanical Ventilation; 3TC: Lamivudine.

Discussion

The use of drugs in pediatric patients in Spain and Europe entails a wide variety of legal administrative situations related to drug procurement and funding. Drugs are frequently prescribed and administered without any solid evidence being available of their efficacy and safety. This does not necessarily mean an inadequate use of drugs, as in most cases, their use is supported by extensive clinical experience and scientific evidence and is established in standard protocols.

This diversity poses a challenge to pediatricians and pediatric pharmacists. Thus, these professionals need to be aware of the specific status of each drug, the arrangements required by current regulations, and medical and legal responsibilities related to the off-label use of drugs in children (clinical trials or compassionate drug use). It is necessary that clinical trials are performed in the pediatric population to provide clinicians with tools that ensure a safe and effective use of drugs in this population.

The results obtained in this study demonstrate a growing tendency to approve therapeutic indications for the pediatric population. However, there are still some funding and marketing problems that need to be overcome. Although indications for pediatric use are most frequently approved by extension, there are an increasing number of new drugs that already include clinical trials and potential indication for pediatric patients.

On another note, the increasing complexity of pediatric therapeutics makes it necessary that pharmacies in pediatric hospitals play a proactive role in the development of standard protocols approved by regulatory authorities (committees for the rational use of medicines and pharmacy) to establish and facilitate therapeutic procedures in pediatrics.

An increasing number of drugs are approved for pediatric use every year. However, there are still a number of funding and marketing barriers that need to be overcome to facilitate access to effective, safe pediatric treatments.

Contribution to the scientific literature

This study contributes relevant information about the considerable efforts made by the scientific community to develop new pediatric drugs and extend indications to pediatric use. This intense activity responds to changes in European laws and regulations on the development of drugs for pediatric use. This study provides a picture of the state of affairs in drugs for pediatric use. In our opinion, it is worth sharing this information with the interested professionals, especially pediatricians.

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Authorship declaration

Lucía Yunquera Romero and Carmen Gallego Fernández contributed to study conception and design. Juan Diego Paradas Palomo contributed to data collection and analysis. Drafting of the manuscript was carried out by three authors: Lucía Yunquera Romero drafted the Introduction and Methods section; Juan Diego Paradas Palomo drafted the Results, and Carmen Gallego Fernández drafted the Discussion. Finally, three authors reviewed critically the manuscript.

Conflict of interest

None declared.

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