Essential List of Medicinal Products for Rare Diseases – Recommendations from the IRDiRC Rare Disease Treatment Access Working Group

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Abstract

Background

Treatments are often unavailable for rare disease patients, especially in low-and-middle-income countries. Reasons for this include lack of financial support for therapies and onerous regulatory requirements for approval of drugs. Other barriers include lack of reimbursement, administrative infrastructure, and knowledge about diagnosis and drug treatment options. The International Rare Diseases Research Consortium set up the Rare Disease Treatment Access Working Group with the first objective to develop an essential list of medicinal products for rare diseases.

Results

The Working Group extracted 215 drugs with Orphan designation in the FDA, EMA databases and/or China's Rare Diseases Catalog. The drugs were organized in seven disease categories: metabolic, neurologic, hematologic, anti-inflammatory, endocrine, pulmonary, and immunologic, plus a miscellaneous category.

Conclusions

The proposed list of essential medicinal products for rare diseases is intended to initiate discussion and collaboration among patient advocacy groups, health care providers, industry and government agencies to enhance access to appropriate medicines for all rare disease patients throughout the world.

Introduction

A significant unmet need for individuals living with rare diseases is access to beneficial therapies, even those that are approved by major regulatory bodies and are considered as standards of care by experts throughout the world. This issue is especially apparent in low-and-middle-income countries (LMICs) but also affects a substantial proportion of eligible patients in high-income jurisdictions. Of course, this inequity in access applies not only to rare disease drugs but also therapies for common, chronic diseases. However, the disparity is even greater for rare disease treatments. Moreover, while there are international initiatives and programs to make available therapies for conditions affecting large patient populations, such as diabetes, HIV and cancer, there has been little action to improve access to drugs for those suffering from rare conditions.

To stimulate a broad response to this unmet need, the International Rare Diseases Research Consortium (IRDiRC) established the Rare Disease Treatment Access Working Group (RDTAWG) with three aims: 1) To improve standards of care for RD patients by promoting access to approved medicines; 2) To initiate

research into the barriers to accessing RD drugs, especially in LMICs; and 3) To define opportunities to address those barriers.

This paper is the first of a three-part series with special focus on lack of access to orphan and rare disease drugs in LMICs and also inequitable access in high-income countries. This first paper presents a curated list of medicines considered to be essential for rare disorders. The second paper will discuss the barriers to access stratified by types of therapy, characteristics of rare disease populations, and key country parameters such as investment in health, health system capabilities, and rare disease priorities. That paper will also review some existing mechanisms for providing therapeutic access for rare and non-rare conditions. The third paper will consider strategies for improving access directed toward barriers identified along the patient pathway, in general and specific to rare conditions.

Methods

The IRDiRC RDTAWG developed a list of essential medicinal products for rare conditions; the list was not intended to include all medicines used to treat rare diseases but those that could be considered as essential based on approvals by key regulatory agencies in the USA, the European Union (EU) and China for the treatment of rare conditions. Two approaches were used to compile the list. The first approach was to start with databases of medicinal products with designated orphan status and/or marketing authorizations for rare disease indications. The initial references were the USA FDA Orphan Drug Product Designation database for products approved in the USA [1], the Orphanet list of Orphan Medicinal Products (OMPs) in Europe (2020) [2], and the EMA database of approved products and designations [3]. All drugs with orphan designations and FDA approval were extracted and a list arranged by generic (medicinal) name, rare condition usage and regulatory approval status was created. Medicinal products for rare diseases that have European Community marketing authorizations were then collated by using the Orphanet and EMA databases. To round out the list, China's recently published Rare Diseases Catalog [4,5] of 121 rare diseases was consulted to develop a list of medicines that were approved for the treatment of recognized rare conditions.

The second approach to developing the essential rare disease medicines list was to start with the World Health Organization Model List of Essential Medicines – 21st list, 2019 [6] and the WHO Model List of Essential Medicines for Children – 7th list, 2019 [7] to extract all essential medicines that were indicated for the treatment of rare diseases. This exercise identified medicines on the FDA, EU, and/or China lists that were also on the WHO essential medicines lists; however, the WHO indication was often not for a rare disease but a more common condition. Some key exceptions are medicines for treating hemophilia, cystic fibrosis, Marfan syndrome, Prader-Willi syndrome, myasthenia gravis, and sickle cell disease. It is important to note that this list does not include any rare cancer drugs. Given the large number and the uniqueness, rare cancers deserve a separate list.

The list of medicinal products was collated by eliminating duplicates and combining medicines that were ostensibly versions of a single drug therapy. The RDTAWG identified as an initial goal the creation of a list

of RD medicines that, based on orphan designation and approval or marketing authorization, were efficacious, safe and having a significant impact on the quality and/or duration of life. In some cases, they could be considered standards of care based on widespread and long-term use; however, no attempt was made to categorize the drugs according to life-saving, curative, or beneficial properties. Moreover, while it was desirable that the medicines on the list could be managed across a variety of countries at different stages of health system development, there was no detailed assessment on the basis of cost-effectiveness, complexity of management, or requirements for administration. Hence, unlike the WHO list of essential medicines, this list of RD drugs is not stratified nor prioritized on the basis of various criteria that could affect feasibility of adoption.

This list is intended to be the initial iteration of a “living document”, to be revised and updated periodically. The list is not based on definitive criteria for inclusion nor is it the product of an expert consensus process. It is not intended to be comprehensive but is proposed to the rare disease community for consideration and uptake as well as a starting point or guide for jurisdictions to set policies on provision of rare disease medicines to their populations.

The members of the RDTAWG reviewed those medications within their area(s) of expertise and, specifically, to eliminate duplicate or redundant medicines, remove drugs considered inappropriate or ineffective, add other drugs that should be on the list, and provide comments as appropriate.

Results

The Table 1 presents the current working list of essential rare disease medicines with different versions of a medication listed separately where appropriate. The list is organized into seven disease categories: metabolic, neurologic, hematologic, anti-inflammatory, endocrine, pulmonary, and immunologic, plus a miscellaneous category. Within each category, drugs are listed by subgroupings and specific conditions, with multiple indications where appropriate. The drugs are not coded in terms of priority, therapeutic strength or equivalence, need for specialized diagnosis or care, or any restrictions (cf. WHO Model List of Essential Medicines). The greatest number of drugs is in the metabolic disease category, but various neurological diseases are extensively represented.

Discussion

Individuals with rare diseases encounter many challenges along the path to appropriate care and treatment. The first obstacle for many is obtaining an accurate diagnosis, which often takes more than five years [8]. For many, the next hurdle involves finding expert care and treatment, which can vary depending upon many factors including geographic location and socioeconomic status. In fact, researchers have noted profound disparities across the globe in access to rare disease medicines, with significant impact on health outcomes and quality of life [9–11]. In 2006, Stolk et al. [12] called for inclusion of RD drugs as essential medicines, but this has not occurred.

Many of the drugs in our RD drug list are not included in the WHO Essential Medicines List. Moreover, not all of the drugs on our list are approved across all jurisdictions, and a few with regulatory approval and/or marketing authorization are not indicated for the specified rare disease(s), even if they are recognized as appropriate or a standard of care. Based upon such a lack of indication, some health systems may choose to deny reimbursement even if the drug is inexpensive, genericized and in distribution. This problem affects patients in high-income as well as low-and-middle income countries. Therefore, it is important to take a broader contextual approach to understand the challenges rare disease patients are facing and address them collectively and systematically.

Approximately one-third of all persons worldwide, including those in low-income but increasingly middle-income countries, do not have access to essential medicines, specifically drugs, vaccines, and diagnostics for communicable, noncommunicable, social-behavioral illnesses, and emerging environmentally induced diseases [13]. The cause of the problem, like the cause of the diseases, is multifactorial and requires not only multidisciplinary and multisectoral approaches but integrated, holistic innovative solutions. Barriers at the individual level include the lack of health literacy, awareness of therapies, and advocacy capacity. Healthcare professionals similarly may lack awareness of appropriate medicines, knowledge to use effectively, and capacity to advocate for access. Major impediments at the systems level include lack of low-cost alternatives (generics and biosimilars) as well as the lack of regulatory, clinical and infrastructure capacity to make complex innovative therapies available and to deliver them to patients [14]. In addition, while nations are criticized for limited national commitment to healthcare and insufficient investment in universal health coverage, they also levy criticism on industry for the lack of transparency and unreasonably high drug prices that compromise their ability to deliver optimal healthcare as punctuated by the WHO resolution on disclosure of drug prices [15].

Many of the aforementioned challenges (especially regulatory expertise and clinical capacity) have a disproportionate impact on rare disease drugs and patients, but there are additional barriers. Some are grounded in “high evidential uncertainty” in extending clinical trial data to real-world outcomes. This is highly problematic in countries that apply “traditional” health technology assessment (HTA) or value-based assessment (VBA) methodology to RD therapies compared to those jurisdictions that use supplemental processes with greater flexibilities that treat RD treatments differently [16].

How could this list of RD medicines be used? A potential pathway is one based on EMA’s EU-Medicines4all (EUM4all) procedure. EMA established EUM4all to provide expert reviews on benefits and risks of medicines that would be used outside the EU, with emphasis on LMICs [17]. Subsequent analysis found that 138 regulatory approvals had been granted in 90 different countries worldwide for six medicines based on EUM4all opinions, with acknowledged great public health impact.

The EUM4all initiative dealt with a broad range of medicines with high impact in LMICs, but we propose that the procedure could profitably be applied to RD medicines. This paper is intended to elicit suggestions and call for collaborations on how to modify, disseminate, and use the list of medicines in the Table 1. Specifically, the RDTAWG seeks input from RD advocacy groups, healthcare providers,

pharmaceutical companies, and government agencies. Subsequent actions include a conference to bring together key stakeholders to elaborate on the list, identify barriers and opportunities for application and collaborate on next steps. The ultimate goal is to enhance access to appropriate medicines for all rare disease patients throughout the world.

Conclusions

The limited number of approved therapeutic options, combined with the unavailability of existing treatments, significantly impair the life of rare disease patients in LMICs. While many countries have recently developed policies and regulations for rare diseases and orphan drugs, access to treatment remains variable among LMICs. With the vision of leaving no one behind, the IRDiRC RDTAWG used the FDA, EMA databases and China's Rare Diseases Catalog to extract approved drugs with orphan designations and create the first list of 215 essential medicinal products for rare diseases. The list was organized into seven disease categories, excluding rare cancers and rare infectious diseases. The ultimate goal of this list is to further stimulate interactions among patient organizations, health care providers, industry and government agencies to improve standards of care for rare diseases by promoting access to treatments.

Declarations

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Availability of data and materials: The datasets analysed as sources for the lists are available from the corresponding author upon request.

Ethics approval and consent to participate: The study does not involve human participants, human data or human tissue. No ethics approval and consent were required.

Consent for publication: The study does not contain any individual person's data.

Authors Contribution: The RDTAWG was led by WG and DWR. WG extracted all the drugs with orphan designations and FDA approval, and initiated the redaction of the manuscript. SG revised the list of drugs extracted by WG. VH used the Orphanet and EMA databases to collate medicinal products for rare diseases that have European Community marketing authorizations. RY consulted China's Rare Diseases Catalog of 121 rare diseases to identify the drugs approved for the treatment of recognized rare conditions. WG, DWR, SG, VH, RY, GZ revised the list of medicinal products, edited the manuscript and validated its final version.

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Abbreviations

IRDiRC: International Rare Diseases Research Consortium

RDTAWG: Rare Disease Treatment Access Working Group

RD: Rare Diseases

LMICs: Low-and-Middle-Income Countries

OMP: Orphan Medicinal Products

FDA: US Food and Drug Administration

EMA: European Medicines Agencies

WHO: World Health Organization

EU: European Union

HTA: Health Technology Assessment

VBA: Value Based Assessment

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Table

Table 1 – Essential list of medicinal products for rare diseases (to be included after the Results section)

	Drug	Condition	Approvals
Metabolic			
		Aminoacid Disorders	
	Benzoate and phenylacetate	Hyperammonemia of urea cycle disorders	FDA
	Sodium phenylbutyrate	Urea cycle disorders	FDA, EMA
	Carglumic acid	N-acetylglutamate synthetase deficiency	FDA, EMA
	Betaine	Homocystinuria	FDA, EMA
	Sapropterin	Hyperphenylalaninemia, Tetrahydrobiopterin deficiency	FDA, EMA, China
	Pegvaliase	Phenylketonuria	FDA, EMA
	Nitisinone	Tyrosinemia type 1	FDA, EMA
		Lysosomal Storage Diseases	
	Miglustat	Gaucher disease	FDA, EMA, China
	Eliglustat	Gaucher disease type 1	FDA, EMA
	Velaglucerase alfa	Gaucher disease type 1	FDA, EMA
	Imiglucerase	Gaucher disease type 1 or Type 3	FDA, EMA, China
	Taliglucerase	Gaucher disease	FDA, EMA
	Agalsidase beta	Fabry disease (alphagalactosidase A deficiency)	EMA, China
	Agalsidase alfa	Fabry disease (alphagalactosidase A deficiency)	EMA, China
	Migalastat	Fabry disease	FDA, EMA
	Sebelipase alfa	Lysosomal acid lipase deficiency, Wolman disease, Cholesteryl ester storage disease	FDA, EMA
	Alglucosidase alfa	Pompe disease	FDA, EMA, China
	Velmanase alfa	Alpha mannosidosis	EMA
	Laronidase	Mucopolysaccharidosis I (Iduronidase deficiency)	EMA, China
	Idursulfase	Hunter syndrome (Mucopolysaccharidosis II)	FDA, EMA, China
	Elosulfase alfa	Mucopolysaccharidosis IV (Morquio A syndrome)	FDA, EMA, China
	Galsulfase	Mucopolysaccharidosis VI (Maroteaux-Lamy syndrome)	EMA
	Vestronidase alfa	Mucopolysaccharidosis VII (Sly syndrome)	FDA, EMA
	Cerliponase alfa	Neuronal ceroid lipofuscinosis type 2	FDA, EMA

Cysteamine	Nephropathic cystinosis	FDA, EMA
Cysteamine (enteric coated)	Nephropathic cystinosis	FDA, EMA
Cysteamine hydrochloride eyedrops	Corneal crystal accumulation in cystinosis	FDA, EMA
	Cholesterol, Lipid, Fatty Acid Disorders	
Evolocumab	Homozygous familial hypercholesterolemia	FDA, EMA, China
Rosuvastatin calcium	Homozygous hypercholesterolemia	FDA, China
Lomitapide	Homozygous familial hypercholesterolemia	FDA, EMA
Cholic acid	Cholesterol and bile acid synthesis defects	FDA, EMA, China
Chenodeoxycholic acid	Cerebrotendinous xanthomatosis	EMA
Volanesorsen	Familial chylomicronemia syndrome	EMA
Tocofersolan	Congenital or hereditary chronic cholestasis	EMA
	Other Metabolic Disorders	
Asfotase alfa	Pediatric onset hypophosphatasia	FDA, EMA
Burosumab-twza	Hypophosphatemic rickets (x-Linked)	FDA, EMA
Calcium acetate	Hyperphosphatemia in renal failure	FDA
Alendronate	Osteogenesis imperfecta	China
Ascorbic acid	Scurvy	FDA
Thiamine	Metabolic acidosis	EMA
Trisodium citrate	Metabolic acidosis	EMA
Levocarnitine	Genetic carnitine deficiency	FDA, China
Triheptanoin	Fatty acid oxidation disorders	FDA
Riboflavin	Acyl Coenzyme A dehydrogenase deficiency	EMA
Uridine triacetate	Hereditary orotic aciduria	FDA
Potassium citrate	Prevention of uric acid nephrolithiasis.	FDA
Tiopronin	Prevention of cystine nephrolithiasis (cystinuria)	FDA
Penicillamine	Wilson disease	China
Trientine HCl	Wilson disease intolerant of penicillamine	FDA, EMA
Zinc acetate	Wilson disease	FDA, EMA
Hydroxocobalamin	Acute cyanide poisoning, Cobalamin defects	FDA
Sodium nitrite/sodium thiosulfate	Cyanide poisoning, Calciphylaxis	FDA
Acetylcysteine	Acetaminophen overdose	FDA
Allopurinol sodium	Preservation of cadaveric kidneys for transplantation	FDA

Neurologic

	General	
Inotersen	Hereditary transthyretin amyloidosis polyneuropathy	FDA, EMA
Tafamidis	Transthyretin amyloidosis	FDA, EMA
Patisiran sodium	Hereditary transthyretin amyloidosis	FDA, EMA
Teriflunomide	Multiple Sclerosis	EMA, China
Fingolimod HCl	Multiple Sclerosis	EMA, China
Siponimod	Multiple Sclerosis	China
Rasagiline	Parkinson Disease (Young and Early-onset)	EMA, China
Selegiline	Parkinson Disease (Young and Early-onset)	FDA, EMA, China
Pramipexole	Parkinson Disease (Young and Early-onset)	EMA, China
Carbidopa/Levodopa	Parkinson Disease (Young and Early-onset); biopterin defects	FDA, EMA
Pitolisant	Narcolepsy with or without cataplexy	FDA, EMA
Sodium oxybate	Narcolepsy with cataplexy	FDA, EMA
Deutetrabenazine	Huntington Disease	China
Tetrabenazine	Huntington Disease	FDA, EMA
Baclofen	Dystonia, Spasticity	FDA
Capsaicin	Postherpetic neuralgia	FDA
Naltrexone	Postherpetic neuralgia	FDA
Ziconotide	Chronic pain requiring intrathecal analgesia	EMA
Everolimus	Tuberous Sclerosis Complex	FDA, EMA
Folic acid	Spina bifida (prevention)	EMA
Biotin	Biotinidase deficiency	China
	Epilepsy	
Vigabatrin	Infantile spasms	FDA, EMA
Rufinamide	Lennox-Gastaut syndrome	FDA, EMA
Cannabidiol	Lennox-Gastaut syndrome and Dravet syndrome	FDA, EMA
Stiripentol	Severe myoclonic epilepsy in infancy (Dravet syndrome)	FDA, EMA
Midazolam	Status epilepticus	FDA
Levetiracetam	Juvenile myoclonic epilepsy, Generalized epilepsy	EMA
Clobazam	Complex and rare disease epilepsy	FDA
Lamotrigine	Complex and rare disease epilepsy	FDA
Topiramate	Complex and rare disease epilepsy	FDA

		Neuromuscular Diseases	
	Gabapentin	Amyotrophic lateral sclerosis	FDA
	Riluzole	Amyotrophic lateral sclerosis	FDA, EMA, China
	Radicava	Amyotrophic lateral sclerosis	China
	Pyridostigmine Bromide	Myasthenia gravis	China
	Amifampridine	Lambert-Eaton myasthenic syndrome	EMA
	Mexiletine hcl	Non-dystrophic myotonic disorders	EMA
	Nusinersen sodium	5q Spinal Muscular Atrophy	FDA, EMA, China
Hematologic			
		Coagulation Defects	
	Octocog alpha	Hemophilia A (Factor VIII deficiency)	EMA
	Rurioctocog alfa pegol	Hemophilia A (Factor VIII deficiency)	EMA
	Lonoctocog alfa	Hemophilia A (Factor VIII deficiency)	EMA
	Emicizumab	Hemophilia A (Factor VIII deficiency)	FDA, EMA, China
	Damoctocog alfa pegol	Hemophilia A (Factor VIII deficiency)	EMA
	Turoctocog alpha	Hemophilia A (Factor VIII deficiency)	EMA
	Simoctocog alfa	Hemophilia A (Factor VIII deficiency)	EMA
	Moroctocog alpha	Hemophilia A (Factor VIII deficiency)	EMA
	Desmopressin acetate	Hemophilia	FDA, EMA
	Recombinant Factor VIII	Hemophilia A (Factor VIII deficiency)	EMA, China
	Efmoroctocog alfa	Hemophilia A (Factor VIII deficiency)	EMA
	Factor VIII/ von Willebrand factor	von Willebrand disease, Hemophilia A	EMA
	Vonicog alfa	von Willebrand disease	EMA
	Eftrenonacog alfa	Hemophilia B	EMA
	Albutrepenonacog alfa	Hemophilia B	EMA
	Nonacog alpha	Hemophilia B (Factor IX deficiency)	EMA
	Human coagulation factor IX	Hemophilia B (Factor IX deficiency)	EMA
	Nonacog beta pegol	Hemophilia B (Factor IX deficiency)	EMA
	Nonacog gamma	Hemophilia B (Factor IX deficiency)	EMA
	Recombinant Factor IX	Hemophilia B (Factor IX deficiency)	EMA, China
	Eptacog alpha (activated)	Hemophilia (Factor VII deficiency)	EMA
	Recombinant Factor VIIa	Hemophilia (Factor VII deficiency)	EMA

Human coagulation factor X	Factor X deficiency	EMA
Catridecacog	Factor XIII A-subunit deficiency	EMA
Human protein c	Protein C deficiency	EMA
	Anemias	
Hydroxyurea	Sickle cell anemia	FDA
Epoetin alfa	Anemia of end-stage renal disease	FDA
Eltrombopag	Idiopathic thrombocytopenic purpura, Aplastic anemia	FDA, EMA
Deferasirox	Beta thalassemia major	FDA, EMA, China
	Other Hematologic Disorders	
Methylene blue injection	Congenital and acquired methemoglobinemia	FDA
Hemin	Acute intermittent porphyria	FDA
Afamelanotide	Erythropoietic protoporphyria	FDA, EMA
Siltuximab	Multicentric Castleman’s disease	FDA, EMA
Anagrelide hydrochloride	Essential thrombocythemia	FDA, EMA
Ravulizumab	Paroxysmal nocturnal hemoglobinuria	FDA, EMA
Macapegfilgrastim	Severe congenital neutropenia	China
Busulfan	Conditioning for hematopoietic stem cell transplant	FDA, EMA
Thiotepa	Conditioning for hematopoietic stem cell transplant	FDA, EMA
Deferiprone	Iron overload	FDA, EMA
Caplacizumab	Acquired thrombotic thrombocytopenic purpura	FDA, EMA
Romiplostim	Immune (idiopathic) thrombocytopenic purpura	FDA, EMA
Ropeginterferon alfa-2b	Polycythemia vera	EMA
Ruxolitinib	Polycythemia vera	FDA, EMA
Immunoglobulin infusion	Agammaglobulinemia	China

Anti-inflammatory

	Rheumatoid Arthritis	
Methotrexate	Juvenile rheumatoid arthritis	FDA, EMA
Etanercept	Juvenile rheumatoid arthritis	FDA, EMA
Methylprednisolone	Juvenile rheumatoid arthritis	EMA
Adalimumab	Juvenile rheumatoid arthritis, Pediatric ulcerative colitis	FDA
Infliximab	Crohn's disease, Juvenile rheumatoid arthritis, Sarcoidosis	FDA

	Tocilizumab	Pediatric polyarticular juvenile arthritis	FDA, EMA
	Abatacept	Polyarticular juvenile idiopathic arthritis	EMA
	Golimumab	Polyarticular juvenile idiopathic arthritis	FDA, EMA
		Gastrointestinal Inflammation	
	Mesalamine; 5-aminosalicylic acid	Ulcerative colitis	FDA
	Obeticholic acid	Primary biliary cholangitis	FDA, EMA
	Tocofersolan	Hereditary chronic cholestasis	EMA
		Angioedema	
	C1 inhibitor(human)	Hereditary angioedema	EMA
	Icatibant acetate	Hereditary angioedema	FDA, EMA
	Lanadelumab	Hereditary angioedema	FDA, EMA, China
	Danazol	Hereditary angioedema	China
	Tranexamic acid	Hereditary angioedema	FDA, China
	C1-esterase-inhibitor, human	Angioedema due to C1 esterase inhibitor deficiency	FDA
	Conestat alfa	Angioedema due to C1 esterase inhibitor deficiency	EMA
		Other Inflammatory Disorders	
	Colchicine	Multiple sclerosis, Behcet's disease, Familial Mediterranean fever	FDA, China
	Eculizumab	Dermatomyositis, Atypical hemolytic uremic syndrome, Neuromyelitis Optica, Paroxysmal nocturnal hemoglobinuria, Myasthenia gravis	FDA, EMA, China
	Rituximab	Anti-neutrophil vasculitis, Wegener’s granulomatosis, Churg-Strauss Syndrome	FDA
	Canakinumab	Familial Mediterranean fever, Cryopyrin fevers	FDA, EMA, China
	IL-1 Receptor antagonist anakinra	Still's disease, Systemic juvenile arthritis	FDA, EMA
	Cenegermin	Neurotrophic keratitis	FDA, EMA
	Ciclosporin	Vernal keratoconjunctivitis	EMA
	Dexamethasone	Non-infectious uveitis	FDA, EMA
	Rilonacept	Cryopyrin-associated periodic syndromes	FDA, EMA
Endocrine			
	Somatropin for injection	Growth hormone deficiency in children	FDA, EMA
	Octreotide	Acromegaly	FDA
	Lanreotide	Acromegaly	FDA

	Pegvisomant	Acromegaly	FDA, EMA
	Pasireotide	Acromegaly and Cushing's syndrome	FDA, EMA
	Osilodrostat	Endogenous Cushing’s syndrome	FDA, EMA
	Ketoconazole	Endogenous Cushing’s syndrome	EMA
	Hydrocortisone	Adrenal insufficiency	FDA, EMA, China
	Human chorionic gonadotropin	Idiopathic Hypogonadotropic Hypogonadism	EMA, China
	Gonadotropin-releasing hormone	Idiopathic Hypogonadotropic Hypogonadism	EMA, China
	Mecasermin	Primary insulin-like growth factor-1 deficiency	FDA, EMA
	Calcitonin-human for injection	Paget's disease (osteitis deformans)	FDA
	Parathyroid hormone	Hypoparathyroidism	FDA, EMA
	Tasimelteon	Non-24-hour sleep-wake disorder	FDA, EMA
	Metreleptin	Leptin deficiency in lipodystrophy patients	FDA, EMA
	Metreleptine	Familial partial lipodystrophy	EMA
Pulmonary			
		Pulmonary Arterial Hypertension	
	Macitentan	Pulmonary arterial hypertension	FDA, EMA, China
	Tadalafil	Pulmonary arterial hypertension	FDA, EMA
	Ambrisentan	Pulmonary arterial hypertension	FDA, EMA, China
	Nitric oxide	Pulmonary arterial hypertension	FDA, EMA
	Sildenafil	Pulmonary arterial hypertension	EMA, China
	Bosentan monohydrate	Pulmonary arterial hypertension, systemic sclerosis	FDA, EMA, China
	Selexipag	Pulmonary arterial hypertension	FDA, EMA, China
	Iloprost	Pulmonary arterial hypertension	FDA, EMA, China
	Parenteral treprostinil	Pulmonary arterial hypertension	FDA, EMA, China
	Riociguat	Thromboembolic pulmonary hypertension and Pulmonary arterial hypertension	FDA, EMA, China
		Cystic Fibrosis	

	Mannitol	Cystic fibrosis	FDA, EMA
	Ivacaftor	Cystic fibrosis	FDA, EMA
	Tezacaftor/ivacaftor	Cystic fibrosis	FDA, EMA
	Tobramycin	Cystic fibrosis	FDA, EMA
	Aztreonam	Cystic fibrosis	FDA, EMA
	Colistimethate sodium	Cystic fibrosis	EMA
	Lumacaftor / ivacaftor	Cystic fibrosis	FDA, EMA
	Levofloxacin	Cystic fibrosis	EMA
		Other Pulmonary Disorders	
	Pirfenidone	Idiopathic Pulmonary Fibrosis	FDA, EMA
	Nintedanib	Idiopathic Pulmonary Fibrosis	FDA, EMA, China
	Caffeine citrate	Primary apnea of premature newborns	FDA, EMA
Immunologic			
	Pegademase bovine	Enzyme replacement for Adenosine deaminase deficiency (ADA)	FDA
	CD34+ cells transduced with ADA cDNA	Severe combined immunodeficiency, Adenosine deaminase deficiency (ADA)	EMA
	Interferon gamma 1-b	Chronic granulomatous disease	FDA
	Tacrolimus	Prophylaxis of graft-versus-host-disease, Graft rejection	FDA
	Sirolimus	Lymphangioleiomyomatosis, Tuberous sclerosis	FDA, EMA
Miscellaneous			
	Pentamidine isethionate	Pneumocystis carinii pneumonia	FDA
	Cromolyn sodium	Mastocytosis	FDA
	Amiodarone	Ventricular tachycardia	FDA
	Autologous human corneal stem cells	Limbal stem cell deficiency	EMA
	Voretigene neparvovec	Inherited retinal dystrophy	FDA, EMA
	Teduglutide	Short bowel syndrome	FDA, EMA
	Defibrotide	Hepatic veno-occlusive disease, Sinusoidal obstruction	FDA, EMA
	Proteolytic enzymes with bromelain	Deep partial- and full-thickness thermal burns	EMA
	Tolvaptan	Autosomal dominant polycystic kidney disease	FDA, EMA
	Ibuprofen	Patent ductus arteriosus	FDA, EMA

	Dexrazoxane	Anthracycline extravasation	FDA, EMA

Table 1: List of 215 essential medicinal products with orphan designation extracted from the FDA database and/or EMA database and/or Chinas’s Rare Diseases Catalog.