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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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)
### Metabolic

| Drug                        | Condition                                                        | Approvals               |
|-----------------------------|------------------------------------------------------------------|-------------------------|
| **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                |
| Taliglucerase               | Gaucher disease                                                 | FDA, EMA, China         |
| 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) | FDA, China |
| Selegiline | Parkinson Disease (Young and Early-onset) | FDA, EMA, China |
| Pramipexole | Parkinson Disease (Young and Early-onset) | FDA, 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

| Drug                  | Indication                                      | Regulatory Bodies |
|-----------------------|-------------------------------------------------|-------------------|
| Gabapentin            | Amyotrophic lateral sclerosis                   | FDA               |
| Riluzole              | Amyotrophic lateral sclerosis                   | FDA, EMA, China   |
| Radicava              | Amyotrophic lateral sclerosis                   | China             |
| Pyridostigmine        | 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

| Drug                  | Indication                                      | Regulatory Bodies |
|-----------------------|-------------------------------------------------|-------------------|
| 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, China   |
| Recombinant Factor VIII| Hemophilia A (Factor VIII deficiency)           | EMA, China        |
| Efmosoctocog alfa     | Hemophilia A (Factor VIII deficiency)           | EMA               |
| Factor VIII/ von Willebrand factor | von Willebrand disease, Hemophilia A | EMA               |
| Vonicog alfa          | von Willebrand disease                          | EMA               |
| Efrenonacog 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 |
|---------------------------|---------------------|-----|
| Catridecagog             | 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 thrombocytemia                 | 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                        | FDA, EMA |
| Ruxolitinib              | Polycythemia vera                        | FDA, EMA, China |
| Immunoglobulin infusion  | Agammaglobulinemia                       | FDA, EMA, 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 |
| Drug                  | Indication                                                   | Regulatory Authority |
|-----------------------|--------------------------------------------------------------|----------------------|
| **Tocilizumab**        | Pediatric polyarticular juvenile arthritis                   | FDA, EMA             |
| **Abatacept**          | Polyarticular juvenile idiopathic arthritis                  | EMA                  |
| **Golimumab**          | Polyarticular juvenile idiopathic arthritis                  | FDA, EMA             |

**Gastrointestinal Inflammation**
- *Mesalazine; 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)
| Drug                          | Indication                                                                 | Regulators |
|-------------------------------|-----------------------------------------------------------------------------|------------|
| 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               | Idiopathic Hypogonadotropic Hypogonadism                                   | EMA, China |
| gonadotropin                  |                                                                             |            |
| 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**

| Drug                          | Indication                                                                 | Regulators |
|-------------------------------|-----------------------------------------------------------------------------|------------|
| Macitentan                    | Pulmonary arterial hypertension                                             | FDA, EMA,  |
| Tadalafil                     | Pulmonary arterial hypertension                                             | China      |
| Ambrisentan                   | Pulmonary arterial hypertension                                             | FDA, EMA   |
| Nitric oxide                  | Pulmonary arterial hypertension                                             | FDA, EMA   |
| Sildenafil                     | Pulmonary arterial hypertension                                             | EMA        |
| Bosentan monohydrate          | Pulmonary arterial hypertension, systemic sclerosis                         | FDA, EMA,  |
|                                |                                                                             | China      |
| Selexipag                     | Pulmonary arterial hypertension                                             | FDA, EMA   |
| Iloprost                      | Pulmonary arterial hypertension                                             | FDA, EMA   |
| Parenteral treprostinil       | Pulmonary arterial hypertension                                             | FDA, EMA,  |
|                                |                                                                             | China      |
| Riociguat                     | Thromboembolic pulmonary hypertension and Pulmonary arterial hypertension   | FDA, EMA,  |
|                                |                                                                             | China      |

**Cystic Fibrosis**
| Drug                          | Condition                      | Agency(s)    |
|-------------------------------|--------------------------------|--------------|
| 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     |
Table 1: List of 215 essential medicinal products with orphan designation extracted from the FDA database and/or EMA database and/or China’s Rare Diseases Catalog.