WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
Coden USA: WJPRAP Impact Factor 8.63
Volume 15, Issue 5, 377-392. Review Article ISSN 2277–7105

ORPHAN DISEASES AND THEIR PHARMACOLOGICAL MANAGEMENT: DRUG DEVELOPMENT, MECHANISMS OF ACTION, AND MONITORING CONSIDERATIONS

Mr. Mahesh Nilesh Junagade[*1], Dr. Vishal Sunil Gujare[2], Mr. Aditya Rajesh Jakhad[3]

[*1]B. Pharm Student, Swami Vivekanand Sanstha's Institute of Pharmacy, Mungase, Malegaon.

[2]Associate Professor, Department of Pharmaceutics, Swami Vivekanand Sanstha's Institute of Pharmacy, Mungase, Malegaon.

[3]M. Pharm (Regulatory Affairs) Student, R. C. Patel Institute of Pharmacy, Shirpur.

Article Received on 27 Jan. 2026,
Article Revised on 16 Feb. 2026,
Article Published on 01 March 2026,

https://doi.org/10.5281/zenodo.18800928

***Corresponding Author**

Mr. Mahesh Nilesh Junagade

B. Pharm Student, Swami Vivekanand Sanstha's Institute of Pharmacy, Mungase, Malegaon.

How to cite this Article: Mr. Mahesh Nilesh Junagade[*1], Dr. Vishal Sunil Gujare[2], Mr. Aditya Rajesh Jakhad[3]. (2026). Orphan Diseases and Their Pharmacological Management: Drug Development, Mechanisms of Action, and Monitoring Considerations. World Journal of Pharmaceutical Research, 15(5), 377–392.

ABSTRACT

Orphan drugs are pharmaceutical agents developed for the treatment and prevention of rare health conditions, commonly referred to as orphan diseases. These medications are often difficult to obtain because of their high cost and the limited amount of research conducted in this area. The occurrence of rare diseases differs from one country to another, depending largely on population characteristics and demographic factors. The Food and Drug Administration (FDA) has approved more than 770 drugs, including 77 that have received orphan drug designation. Several of these medications, primarily identified and developed by the pharmaceutical industry, are considered highly valuable but are associated with significant expense. The use of orphan drugs requires monitoring of specific clinical parameters. Therapeutic supervision should be tailored according to the patient's physical status and the seriousness of the condition. This review article intends to provide a comprehensive evaluation of the development of orphan drugs and their monitoring practices.

KEYWORDS: Orphan diseases, Orphan drugs-development, Therapeutic monitoring, Disease severity, Monitoring criteria.

INTRODUCTION

Orphan diseases are defined by their rarity and are more commonly observed in regions with large population densities. Their prevalence is generally higher in developing nations compared to developed countries. These conditions are referred to as "orphan" diseases because of the difficulties involved in developing therapies for disorders that affect only a small proportion of the population. Prominent examples of rare diseases include Kahler's disease (Myelomatosis), Hodgkin's lymphoma, Lou Gehrig's disease, Spina bifida, and Apert syndrome, among others. According to the definition followed in the United States, an orphan disease is one that affects fewer than 200,000 individuals.[1]

The worldwide burden of orphan diseases remains considerable, as each nation addresses only a limited segment of the affected population. The diagnosis of rare diseases is frequently complex and prolonged, often taking several years due to limitations in diagnostic techniques and a lack of adequate awareness among healthcare professionals. In many cases, appropriate diagnostic tools are unavailable for numerous rare conditions, further increasing the global challenges associated with these disorders.

In response to such complex circumstances, the development of orphan drugs has become an essential approach. These specialized medicinal products are designed to deliver effective therapeutic interventions for rare diseases, thereby providing targeted treatment options where conventional therapies are limited.[2]

DEVELOPMENT OF ORPHAN DRUGS

Orphan drugs are developed to treat diseases or disorders that occur rarely and face a unique range of obstacles that limit their large-scale production. Because these conditions affect a very small segment of the population, pharmaceutical companies often consider their manufacture economically unviable without government support. Consequently, securing manufacturing approval for orphan drugs becomes extremely challenging, as the high financial burden discourages pharmaceutical industries from investing in their production. These medicines are frequently based on biological products used for the diagnosis, treatment, and prevention of rare diseases and are especially important in resource-limited regions where endemic rare disorders are present.[3]

The availability of orphan drugs in the market remains limited. Although certain pharmaceutical companies continue to invest in research, the process from the identification

of a new drug molecule to its commercial launch is lengthy, uncertain, and requires significant financial resources. Despite their importance in addressing unmet medical needs, orphan drug development carries several drawbacks. The most significant barrier is the exceptionally high cost involved in research, development, and commercialization. Recovering these expenditures through sales is often unrealistic due to the small patient population and limited manufacturing interest. While these medications can be life-saving for a small group of patients, their commercialization remains difficult. To address this issue, governments may provide tax incentives and financial benefits to encourage pharmaceutical companies, as demonstrated in the United States with the implementation of the Orphan Drug Act in 1983 during the presidency of Ronald Reagan.[4]

The FDA also ensures that drugs submitted by private manufacturers comply with all necessary regulatory standards, comparable to those applied to treatments for more common diseases. This regulatory oversight includes both small-molecule drugs in tablet or capsule form and large-molecule biologics derived from living sources, which are regulated under Section 351 of the Public Health Service Act. Over time, the incidence of certain orphan diseases affecting larger patient groups has increased, leading to greater industrial research interest in orphan drug development.

The Orphan Drug Act has significantly contributed to addressing pricing and accessibility issues associated with orphan drugs. Following amendments introduced in 1984, multiple orphan drugs received FDA approval, with nearly 770 drugs identified and authorized in the United States alone. Nevertheless, difficulties continue in developing countries such as India, where a uniform definition of rare diseases is lacking and comprehensive prevalence data remain insufficient.[5]

EXAMPLES OF ORPHAN DISEASES AND ORPHAN DRUGS

Numerous rare diseases are eligible for orphan drug designation, highlighting the critical role of specialized therapies in the management of these uncommon disorders. Prominent examples include Hodgkin's lymphoma, cystic fibrosis, porphyria, myelomatosis, polycythemia vera, encephalomyelitis disseminata, methanol poisoning, spina bifida, acquired hemophilia, graft-versus-host disease (GVHD), chronic myelogenous leukemia, and differentiated thyroid carcinoma (DTC).[6]

Orphan drugs used in the treatment of these rare conditions are listed along with their generic and brand names, offering a detailed overview of important and economically viable therapeutic agents. According to a study conducted by Helfand et al. in 2013, examples of such medications include acetyl cysteine (Lumenac), 4-aminosalicylic acid (Paser), digoxin antibody (Lanoxin), fomepizole (Antizol), factor VIII (Hemorel), human antithrombin III (Thrombate III), thalidomide (Thalomid), erythropoietin (Intas), cyclosporine (Esporine), methotrexate (Remtrex), rituximab (Rituxan), lenalidomide (Revlimid), eculizumab (Soliris), everolimus (Afinitor), nilotinib (Tasigna), bortezomib (Velcade), interferon beta-1a (Avonex), ipilimumab (Yervoy), interferon beta-1a (Rebif), ruxolitinib (Jakavi), carfilzomib (Kyprolis), recombinant factor VIIa (Novo Seven), glatiramer acetate (Copaxone), pemetrexed (Alimta), dasatinib (Sprycel), ivacaftor (Kalydeco), sunitinib malate (Sutent), recombinant anti-hemophilic factor VIII (Kogenate), sorafenib tosylate (Nexavar), and ibrutinib (Imbruvica), among others.

This broad spectrum of orphan drugs reflects continuous efforts to deliver effective therapeutic interventions for rare diseases and demonstrates the expanding pharmacological innovations within the domain of orphan drug development.[7]

ORPHAN DISEASES AND ITS DRUG TREATMENT WITH MONITORING CRITERIA

Hodgkin’s Lymphoma

Hodgkin's lymphoma is categorized as a rare type of cancer that primarily affects the immune system. It causes damage to white blood cells, particularly B-lymphocytes, leading to their malignant transformation. In simpler terms, Hodgkin's lymphoma is a cancer of the lymphatic system in which abnormal B-cells become cancerous and accumulate within the lymph nodes.[8]

The disease develops through three defined stages. In stage 1, cancerous cells are confined to a single lymph node. In stage 2, the malignancy spreads to two or more lymph nodes. By stage 3, the cancer progresses further and may involve lymph nodes on both sides of the diaphragm.

The standard treatment protocol for Hodgkin's lymphoma generally includes a combination of chemotherapy and corticosteroid therapy, such as Prednisolone. This treatment strategy is designed to eliminate malignant cells, inhibit their multiplication, and control disease

progression. Although Hodgkin's lymphoma is an uncommon condition, it requires a well-planned and targeted therapeutic approach to effectively manage its impact on the immune and lymphatic systems.[9]

Myelomatosis

Multiple myeloma, also known as Kahler's disease, is a rare malignancy characterized by the abnormal and uncontrolled proliferation of monoclonal plasma cells, a specific type of white blood cell, within the bone marrow. This excessive growth results in the production of non-functional intact immunoglobulins and immunoglobulin light chains. The impact of multiple myeloma includes bone destruction, weakened immune function, renal impairment, and disturbances in red blood cell production.[10]

This condition significantly affects multiple physiological systems. Common causes of mortality associated with myelomatosis include haemorrhage due to reduced platelet counts, complications related to bone damage, kidney failure, and pulmonary embolism resulting from blood clots in the lungs. The complex and systemic effects of the disease highlight the necessity for thorough understanding and a targeted management strategy for this rare and intricate cancer.

In the management of multiple myeloma, Lenalidomide serves as a key therapeutic agent, recognized for its distinctive mechanism of action. It enhances T-cell co-stimulation, thereby promoting cytotoxic activity against malignant cells. This specific mechanism is intended to suppress the uncontrolled proliferation of monoclonal plasma cells, offering a focused therapeutic approach to reduce the adverse effects of multiple myeloma on the bone marrow, immune system, and essential organs.[11]

Porphyria

This group of syndromes includes disorders characterized by abnormalities in porphyrins, which are essential enzymes involved in the synthesis of heme. When these enzymes do not function properly, the conversion of porphyrin into heme is disrupted, leading to serious manifestations such as hypertension, sleep disturbances, muscle weakness, and anxiety. In addition, patients may present with milder symptoms, including severe pain in the abdomen, back, and limbs. The three main forms of porphyria are acute intermittent porphyria, variegate porphyria, and hereditary coproporphyria, the latter being an uncommon inherited condition.[11]

Hereditary coproporphyria occurs due to the inheritance of a mutated gene from one parent in an autosomal dominant pattern or from both parents in an autosomal recessive pattern.

For therapeutic management, Haemarginate is administered. Its mechanism of action involves restoring heme levels within the body. This treatment is vital for controlling clinical symptoms and correcting the underlying impairment in heme production associated with porphyria.[12]

Chronic myelogenous leukemia

This condition is a rare clonal disorder classified under myeloproliferative neoplasms and is characterized by the excessive proliferation of hematopoietic cells within the bone marrow. The disease advances through three defined stages: chronic, accelerated, and blast phases. During progression, immature white blood cells, referred to as blasts, are detected in both the peripheral blood and bone marrow. One of the prominent and serious clinical manifestations of chronic myeloid leukemia (CML) is bone pain.[13]

Dasatinib is used as a therapeutic agent in the management of CML. It acts by inhibiting abnormal proteins that transmit signals promoting the proliferation of malignant cells. This targeted mechanism helps suppress uncontrolled cellular growth associated with CML, thereby aiding in disease control and reducing symptoms, including bone pain.[14]

Table 1: Orphan drugs overview: Diseases, Affected areas, Categories, Mechanisms, and Monitoring.

Disease	Affected area/ location	Name of the orphan drug with category	Mechanism of action	Monitoring criteria
Hodgkin's lymphoma	White blood cells (over production of B-cells)-immune system	Prednisolone Corticosteroid	Suppress the migration of polymorphonuclear leucocytes ↓ decreases inflammation ↓ suppress the immune function	Monitor the toxic level – inflammation and blood sugar level thoroughly.[23]
Myelomatosis, myelomtics pina bifida	Bone marrow (uncontrolled proliferation of monoclonal	Lenalidomide Immunomodulator agent	Increase T-cell co stimulation ↓ Produces	Monitor the complete blood counts. For first 12 weeks; the test should be done

	plasma cells)		cytotoxicity against tumour cells ↓ Inhibiting the proliferation of malignant cells.	twice a week. Then once in four weeks until the results are normal.[24]
Porphyria	Porphyrin (enzyme responsible for the synthesis of heme)- RBC	Haemarginate Ferric compound	Reduce the overproduction of gamma aminolevulinic acid that produce the acute symptoms of porphyria ↓ Replenishing the heme stores within the body.	Monitor the level of blood through screening tests (blood tests which show whether the blood is properly clotting or not) and clotting factor tests.[25]
Graft versus host disease (GVHD)	Stem cells, bone marrow	Thalidomide Immunomodulatory agent	Inhibiting the production of myeloma cells ↓ By blocking the expression of interlukin 6 (IL 6) ↓ Degradation of protein	Monitor the platelet count of the patients and also BP, blood sugar level, and allergic reactions such as skin rashes. Also perform liver function test and kidney function tests.[26]
Chronic myelogenous leukemia (CML)	WBC, bone marrow	Dasatinib Anti-cancer drug	Blockage of abnormal proteins that signals the cancerous cells to multiply	Perform the tests of blood - complete blood count (CBC) Monitor the interactions when consumed with other Medications.[27]
Cystic fibrosis	Upper and lower respiratory tract	Ivacaftor, Ibrutinib Cystic fibrosis transmembrane conductance regulator (CFTR)	Improve the function of G551D-CFTR gene ↓ Transport of Na+ and Cl- ions across cell membrane ↓ Improves hydration clearing of thick mucus.	Monitor the sodium and chloride ion concentration which produce serious systemic effect and, also monitor the serious adverse event in patients age 18 or older.[28]
Differentiated thyroid	Thyroid gland	Sorafenib Tosylate	Blocks the enzyme RAF kinase	Monitor the liver function tests

carcinoma (DTC)		Kinase inhibitor	↓ Control of cell division or proliferation ↓ Inhibit the tumour growth and angiogenesis of DTC.	regularly, also monitor the symptoms such as burning sensation in tongue or mouth ulcers- if it is, consult your physician.[29]
Polycythemia vera	Red blood cells (RBC)	Ruxolitinib Anti-cancer drug (kinase inhibitor)	Functions mainly to suppress the immune system, decrease the production of RBC	Monitor the patient's RBC level and urea level (should not exceed 23 mg/dl). Monitor the size of the spleen through physical examination. Monitor the ECG levels of the patients and also monitor the severe reactions such as gum bleeding.[30]
Encephalo-myelitis disseminates	Neurons/axon	Glatiramer acetate Immunomodulator	Stimulation of myelin (basic protein) ↓ Insulation of nerve fibres in spinal cord ↓ Blocking of myelin damaging T-cells.	Monitor the platelet count of the patients and also monitor the BP, blood sugar level. Also perform liver function test and kidney function tests.[31]
Acquired hemophilia	RBC	Factor VII A Recombinant - clotting factor	It mainly works by the inhibition of hemorel factor namely factor VIIA recombinant by autoantibodies leads to clotting of blood.	Monitor the activity of anti- thrombin VII A and the hemoglobin value (> or equal to 12 g/dl) and blood pressure value (normal-120/70 mm Hg).[32]

Polycythemia vera

It is a long-term disorder classified under myeloproliferative neoplasms. Commonly known as erythrocytosis, it is characterized by an abnormal elevation in red blood cell mass. The condition involves clonal proliferation of genetically altered stem cells, which also affects white blood cells and platelets. The major clinical concern in polycythemia vera is the increased risk of thrombotic complications due to elevated blood viscosity. Although it

represents a rare form of polycythemia, it may, in certain instances, be associated with progression to leukemia.[15]

The standard treatment for polycythemia vera generally involves the use of Ruxolitinib. This drug works by suppressing immune system activity and reducing excessive red blood cell production. Through this targeted mechanism, it addresses the underlying pathological processes responsible for the disorder.[16]

Differentiated Thyroid Carcinoma

This is a slowly progressive form of thyroid carcinoma and is considered a rare condition that presents as a mass in the thyroid gland. According to the World Health Organization (WHO) classification, it is mainly divided into papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC), with FTC being a less common subtype of differentiated thyroid carcinoma (DTC). The main clinical manifestation is the presence of a benign thyroid nodule. The advised treatment includes the use of Sorafenib tosylate. Prior to initiating this medication, surgical intervention and radioactive iodine therapy are typically recommended. Sorafenib tosylate acts by inhibiting tumour proliferation and angiogenesis in cases of DTC.[17]

Cystic Fibrosis

Cystic fibrosis is an uncommon disorder characterized by multi-organ involvement, mainly affecting the upper and lower respiratory tract and resulting in inflammation. It also impacts the pancreas and the reproductive system. The disease primarily arises due to genetic defects and follows an autosomal recessive inheritance pattern, most commonly caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Its occurrence is more frequent in Caucasian populations, largely due to the presence of two defective CFTR gene mutations.[18]

An early sign of cystic fibrosis is an unusually salty taste of the skin. As the disease progresses, additional symptoms may become more severe over time. Management of the condition includes the administration of Ivacaftor and Ibrutinib. These drugs function by improving the activity of the G551D protein associated with the CFTR gene, thereby aiding in the management of the disease.[19]

Encephalomyelitis Disseminate

Encephalomyelitis disseminates, more widely referred to as multiple sclerosis (MS), is a long-term autoimmune condition marked by inflammation and injury to the central nervous system, specifically the brain and spinal cord. The disorder develops when the immune system erroneously targets the protective myelin sheath that surrounds nerve fibers, thereby interfering with signal transmission between the brain and other parts of the body. This process of demyelination leads to a broad spectrum of clinical manifestations, such as fatigue, loss of coordination, sensory disturbances, and cognitive impairment. Multiple sclerosis commonly follows a relapsing-remitting course, in which symptoms worsen periodically and then improve, although in some cases it may gradually advance to continuous neurological deterioration. The precise etiology of MS remains uncertain; however, it is thought to result from an interplay of genetic susceptibility and environmental influences. Treatment generally consists of immunomodulatory therapies aimed at symptom control and slowing disease progression.[20]

Waldenstrom Macroglobulinemia

Waldenstrom macroglobulinemia is an uncommon malignancy categorized as a chronic lymphoproliferative disorder that primarily involves white blood cells. It is marked by excessive production of immunoglobulins and is classified among malignant gammopathies. The disease mainly affects two subsets of B-cells: lymphoplasmacytoid cells and plasma cells. In this condition, the bone marrow produces an abnormally high number of white blood cells, which accumulate and interfere with normal, healthy blood cells.

The preferred treatment for Waldenstrom macroglobulinemia is Ibrutinib. This medication works by inhibiting protein kinase activity, thereby targeting the fundamental pathological mechanisms responsible for the disease.

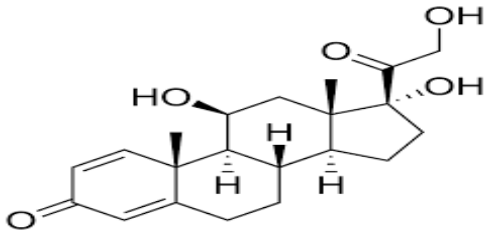
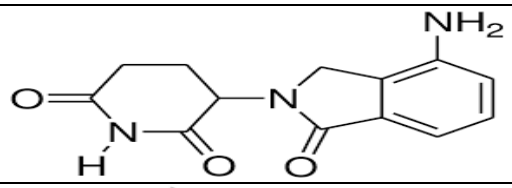
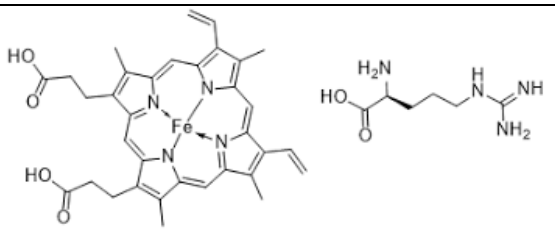
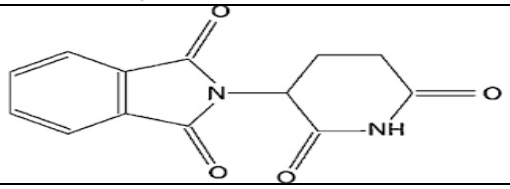
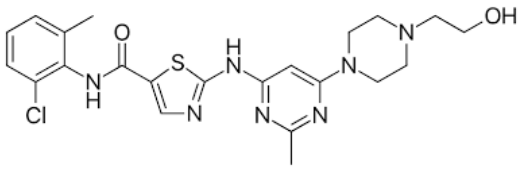
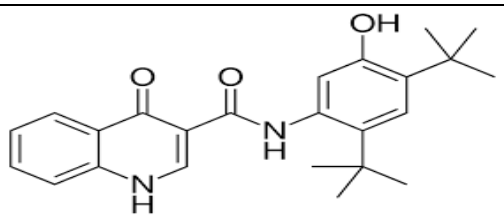
Acquired Haemophilia

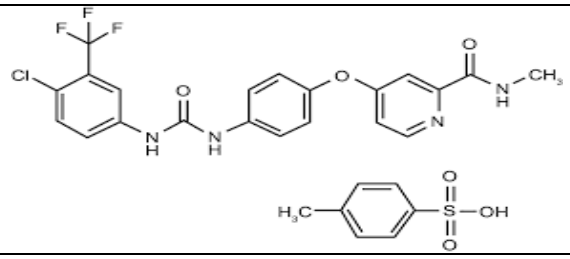
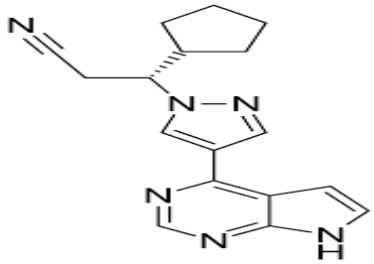
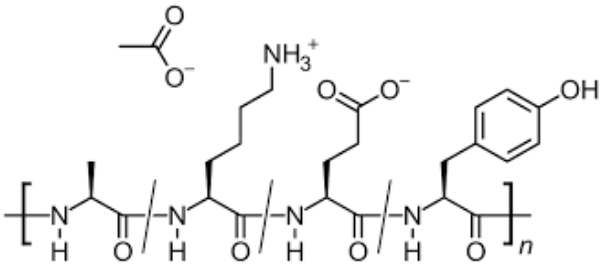
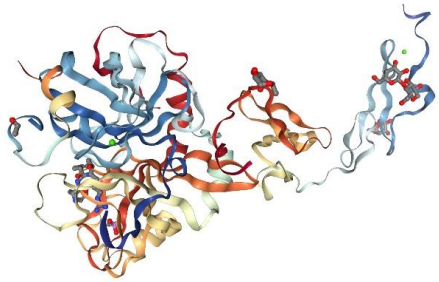
Acquired haemophilia is an uncommon yet severe autoimmune condition characterized by the sudden formation of inhibitors that target and inactivate clotting factor VIII, an essential protein required for normal blood coagulation. In contrast to congenital haemophilia, which is inherited and present at birth, acquired haemophilia generally develops later in adulthood. This disorder can result in excessive and uncontrolled bleeding, both internal and external, presenting with manifestations such as easy bruising, extended bleeding after minor trauma,

and in critical situations, potentially fatal hemorrhages.[21] Acquired haemophilia is frequently linked to underlying illnesses, autoimmune diseases, or the use of certain medications.

Diagnosis involves measuring clotting factor levels and identifying the presence of specific inhibitors. The primary objectives of treatment are to manage bleeding episodes and eradicate the inhibitors, commonly through the use of immunosuppressive therapy and clotting factor replacement. Effective management requires a multidisciplinary approach, involving haematologists, immunologists, and other healthcare professionals to address the complex characteristics of this acquired bleeding disorder.[22]

Table 2: Chemical Structures of Orphan Drugs.

Orphan Disease	Orphan Drug Used	Structure
Hodgkin's lymphoma	Prednisolone	
Myelomatosis, Myelomtics Pina Bifida	Lenalidomide	
Porphyria	Heme Arginate	
Graft Versus Host Disease (GVHD)	Thalidomide	
Chronic Myelogenous Leukaemia (CML)	Dasatinib	
Cystic fibrosis	Ivacaftor	

Differentiated thyroid carcinoma (DTC)	Sorafenib Tosylate	
Polycythemia Vera	Ruxolitinib	
Encephalomyelitis Disseminates	Glatiramer Acetate	
Acquired Hemophilia	Factor VII A	

MONITORING CRITERIA FOR ORPHAN DRUGS

The following factors should be considered when administering orphan drugs: the patient's specific physiological status, the approved indication of the drug, its mechanism of action, and the potential adverse effects associated with its use.

1) Patient's Individual Body Conditions

Before administering an orphan drug, the patient's overall physiological status must be carefully evaluated. This includes age, body weight, organ function (particularly liver and kidney function), immune status, and presence of comorbid conditions. Since many orphan drugs are potent and highly specific, variations in metabolism and drug clearance can significantly influence therapeutic outcomes. Individualized assessment helps in optimizing dosage, minimizing toxicity, and impr`oving treatment response.

2) Indication of the Particular Drug

The specific clinical indication for which the orphan drug is prescribed must be clearly established. Orphan drugs are typically approved for narrowly defined rare conditions, and their use outside approved indications requires strong clinical justification. Understanding the exact disease stage, severity, and patient eligibility criteria ensures appropriate utilization. Proper indication-based prescribing enhances therapeutic efficacy and prevents misuse.

3) Mechanism of Action of the Drug

A thorough understanding of the drug's mechanism of action is essential for effective monitoring. Many orphan drugs act on highly specific molecular targets, such as genetic mutations, enzymes, or signalling pathways. Knowledge of how the drug interacts at the cellular or molecular level assists clinicians in predicting therapeutic benefits and possible complications. It also helps in assessing treatment response and identifying resistance or treatment failure.

4) Adverse Reactions Produced by the Drug

Monitoring for adverse drug reactions is critical due to the limited clinical exposure and smaller trial populations associated with orphan drugs. Some adverse effects may only become evident during post-marketing surveillance. Regular clinical evaluation, laboratory investigations, and patient reporting are necessary to detect early signs of toxicity. Timely identification and management of adverse reactions ensure patient safety and long-term treatment success.

CONCLUSION

In conclusion, the advancement of orphan drugs has emerged as an essential approach in managing the distinct challenges associated with rare diseases. These disorders, frequently neglected because of their low prevalence, demand specialized treatment options to deliver targeted therapy and improved outcomes for affected patients. The Orphan Drug Act in the United States has significantly encouraged pharmaceutical companies to invest in orphan drug research and development, resulting in the approval of more than 770 drugs granted orphan designation.

Despite this progress, several obstacles remain, particularly in developing nations such as India, where a uniform definition of rare diseases is lacking and comprehensive prevalence data are insufficient. The substantial financial burden linked to orphan drug research and

development continues to be a major barrier. Therefore, governments across the globe must adopt supportive measures, including tax incentives and policy benefits, to motivate pharmaceutical industries to participate in this critical area of research.[33] With ongoing advancements in orphan drug development, it is essential for healthcare professionals and regulatory authorities to work collaboratively in strengthening monitoring systems. Such coordination ensures that patients with rare diseases receive appropriate and effective care, reducing disease-related challenges and improving long-term outcomes for individuals affected by orphan conditions.

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