Progression of Orphan Therapeutics: Metabolic Disorders

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Graphic Displays of Approved Orphan Drugs for Metabolic Disorders, Sorted by ICD-10 Disease Classification and Years of Approval
Introduction

**Background** – Since the passage of the *Orphan Drug Act* on January 4, 1983, a total of 481 orphan drugs have been approved by the FDA, based on FDA’s *Orphan Drug Designations and Approvals* database.\(^1\) The objective of the Orphan Drug Act is to promote the development of treatments for rare diseases; a rare disease is defined as a disease with <200,000 patients in the US. This legislation provides economic incentives for pharmaceutical manufacturers, consisting principally of the following three incentives: seven years of market exclusivity; tax credits for certain development costs; and a waiver of application filing fee.

**Purpose** – The purpose of this project on the *Progression of Orphan Therapeutics: Metabolic Disorders* is to develop graphic displays of approved orphan drugs for a given category of rare diseases. Considering the variety of orphan drug approvals, the huge number and variety of rare diseases, and the current lack of a comprehensive coding system incorporating rare diseases, for the purposes of this project it was decided to focus on metabolic disorders and to use the International Classification of Diseases (ICD), although the current version is not optimized with respect to rare diseases or orphan drugs. With this caveat in mind, between 1983 and 2014, there were a total of 45 orphan drug approvals for rare Metabolic Disorders, as classified by WHO’s *ICD-10 Version:2015*\(^2\), representing 9.4% of all orphan drug approvals during this time period.

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Approved Orphan Drugs for Rare Metabolic Disorders – A list of the approved orphan drugs of interest was developed from the above referenced FDA’s Orphan Drug Designations and Approvals\(^1\) database, searching by approved products, and cross-checking against the list of rare Metabolic Diseases, based on the above referenced WHO’s ICD-10 Version:2015\(^2\) classification system for rare Metabolic Disorders (categories E70-E89).

In contrast to our report on the Progression of Modern Therapeutics (2014 Report)\(^3\), where included drugs were limited to the first approved drugs (listed by their proprietary names) for a given new molecular entities (NME’s), in the present report all relevant orphan drug approvals were included and listed by their proprietary names. Older drugs, which are listed for reference, as appropriate, are typically summarized by general pharmacologic classes or established names. Subsequently, FDA’s Drugs@FDA\(^4\) database was consulted for drugs of interest, including for approval dates and approved indications.

The general mechanism of action for approved orphan drugs for specific metabolic disorders is listed under the name of each disorder.

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Methods, cont.

Graphs – The graphic displays for individual rare Metabolic Disorder categories (ICD-10 categories E70 through E89) were developed using Omni’s Omnigraffle Pro on an iMac computer. Other graphs were generated using Microsoft Office:Mac’s Excel.

On each graph, corresponding to a given category of Metabolic Disorders, e.g., *E70 Disorders of Aromatic Amino Acid Metabolism*, the individual approved orphan drugs are represented by colored circles on the X-axis showing their year of approval.

The numbers on the right hand side, e.g., *6 / 23 Y & 4 M*, represent the number of approved orphan drugs per specific Metabolic Disorder and the number of years and months from the first to the latest approval for that disorder.

On the left hand side are listed the ICD-10 decimal codes, within the specific category of Metabolic Disorders of interest and their subcategories, e.g., *E70.2 Disorders of Tyrosine Metabolism*. The names of subcategories with approved orphan drugs are highlighted.

Note that graphs for the following six Metabolic Disorder categories are not included, since they do not have any approved orphan drugs:

- Lactose Intolerance (E73)
- Disorders of Glycoprotein Metabolism (E77)
- Disorders of Purine and Pyrimidine Metabolism (E79) (excluding gout)
- Volume Depletion (E86)
- Other Disorders of Fluid, Electrolyte and Acid-Base Balance (E87)
- Postprocedural Endocrine and Metabolic Disorders, Not Elsewhere Classified (E89)
Disclaimer and Waiver

Disclaimer and Waiver – The information presented in this report on the Progression of Orphan Therapeutics: Metabolic Disorders is intended for the purpose of providing graphic displays of approved orphan drugs between 1983 and 2014 for rare Metabolic Disorders as listed under ICD-10 and years of approval. It is not intended for any other purpose, including but not limited to advice on drug treatment or drug selection. To that extent, users of this report and the information it contains affirm an understanding of the report’s purpose and release the Therapeutics Research Institute from any claims arising out of their use of this report.

Considering the challenges in sorting the necessary data for this report as similarly constructed graphics displays have not been publicly available to date, it’s inevitable that there will be some errors and omissions. Thus, the absence of any specific approved drug in no way implies they are not listed because of some hidden criteria. Such errors and omissions will be corrected in future updates, as appropriate.
Progression of Orphan Therapeutics
Metabolic Disorders (E70-E90)
Disorders of Aromatic Amino Acid Metabolism (E70)

Older Drugs for Disorders of Aromatic Amino Acid Metabolism

n/a

E70.0 Classical Phenylketonuria
E70.1 Other Hyperphenylalaninemas
E70.2 Disorders of Tyrosine Metabolism
E70.3 Albinism
E70.8 Other Disorders on Aromatic Amino Acid Metabolism
E70.9 Disorders of Aromatic Amino Acid Metabolism, Unspecified

Phenylketonuria (E70.0)
PAH Co-factor

Tyrosinemia Type I (E70.2)
HPPD Enzyme Inhibition

ORPHAN DRUG ACT OF 1983

Year of Approval
Progression of Orphan Therapeutics
Metabolic Disorders (E70-E90)
Disorders of Branched-Chain Amino Acid Metabolism and Fatty-Acid Metabolism (E71)

Older Drugs for Disorders of Branched-Chain Amino Acid Metabolism and Fatty Acid Metabolism
n/a

E71.0 Maple-Syrup Urine Disease
E71.1 Other Disorders of Branched Chain Amino Acid Metabolism
E71.2 Disorders of Branched-Chain Amino Acid Metabolism, Unspecified
E71.3 Disorders of Fatty Acid Metabolism

Primary Systemic Carnitine Deficiency (E71.3)
Supplement

ORPHAN DRUG ACT OF 1983

Year of Approval
Progression of Orphan Therapeutics
Metabolic Disorders (E70-E90)
Other Disorders of Amino Acid Metabolism (E72)

Older Drugs for Other Disorders of Amino Acid Metabolism
Penicillamine (Cystinuria)
Cuprimine (1970)
Depen (1978)

E72.0 Disorders of Amino Acid Transport
E72.1 Disorders of Sulfur-Bearing Amino Acid Metabolism
E72.2 Disorders of Urea Cycle Metabolism
E72.3 Disorders of Lysine and Hydroxylysine Metabolism
E72.4 Disorders of Ornithine Metabolism
E72.5 Disorders of Glycine Metabolism
E72.8 Other Specified Disorders of Amino Acid Metabolism
E72.9 Disorders of Amino Acid Metabolism, Unspecified

Hyperammonemia (E72.2)
Inhibition of Ammonia Formation

Homocystinuria (E72.1)
Methylation Activation

Cystinosis (E72.0)
Cystine Depletion

Cystinuria (E72.0)
Cystine Chelation

ORPHAN DRUG ACT OF 1983

Year of Approval
Progression of Orphan Therapeutics
Metabolic Disorders (E70-E90)
Disorders of Sphingolipid Metabolism and Other Lipid Storage Disorders (E75)

Older Drugs for Disorders of Sphingolipid Metabolism and Other Lipid Storage Disorders

n/a

E75.0 GM2 Gangliosidosis
E75.1 Other Gangliosidosis
E75.2 Other Sphingolipidosis
E75.3 Sphingolipidosis, Unspecified
E75.4 Neuronal Ceroid Lipofuscinosis
E75.5 Other Lipid Storage Disorders
E75.6 Lipid Storage Disorder, Unspecified

**Fabry Disease (E75.2)**
Enzyme Replacement

**Gaucher Disease Type I (E75.2)**
Enzyme Replacement; Enzyme Inhibitor

ORPHAN DRUG ACT OF 1983

Year of Approval


1/---

6/23 Y & 4 M
Progression of Orphan Therapeutics
Metabolic Disorders (E70-E90)
Disorders of Glycosaminoglycan Metabolism (E76)

Older Drugs for Disorders of Glycosaminoglycan Metabolism
n/a

E76.0 Mucopolysaccharidosis, Type I
E76.1 Mucopolysaccharidosis, Type II
E76.2 Other Mucopolysaccharidoses
E76.3 Mucopolysaccharidosis, Unspecified
E76.8 Other Disorders of Glucosaminsylcian Metabolism
E76.9 Disorders of Glucosaminsylcian Metabolism, Unspecified

**Morquio A Syndrome (MPS IV A) (E76.2)**
Enzyme Replacement

**Hunter Syndrome (MPS II) (E76.1)**
Enzyme Replacement

**Maroteaux-Lamy (MPS VI) (E76.2)**
Enzyme Replacement

**Hurler & Hurler-Scheie Syndrome (MPS I) (E76.0)**
Enzyme Replacement

ORPHAN DRUG ACT OF 1983

Year of Approval

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Progression of Orphan Therapeutics
Metabolic Disorders (E70-E90)
Disorders of Lipoprotein Metabolism and Other Lipidemias (E78)

Older Drugs for Disorders of Lipoprotein Metabolism and Other Lipidaemias

- HMG-CoA Reductase Inhibitors
- Cholesterol Absorption Inhibitors
- LDL Apheresis

E78.0 Pure Hypercholesterolemia
E78.1 Pure Hyperglyceridemia
E78.2 Mixed Hyperlipidemia
E78.3 Hyperchylomicronemia
E78.4 Other Hyperlipidemia
E78.5 Hyperlipidaemia, Unspecified
E78.6 Lipoprotein Deficiency
E78.8 Other Disorders of Lipoprotein Metabolism
E78.9 Disorders of Lipoprotein Metabolism, Unspecified

Homozygous Familial Hypercholesterolemia (E78.0)
MTP Inhibition; ApoB-100 Synthesis Inhibition

ORPHAN DRUG ACT OF 1983

Year of Approval


Juxtapid Kynamro

2/0 Y & 1 M
Progression of Orphan Therapeutics
Metabolic Disorders (E70-E90)
Disorders of Porphyrin and Bilirubin Metabolism (E80)

Older Drugs for Disorders of Porphyrin and Bilirubin Metabolism
n/a

E80.0 Hereditary Erythropoietic Porphyria
E80.1 Porphyria Cutanea Tarda
E80.2 Other Porphyria
- E80.3 Defects of Catalase and Peroxidase
- E80.4 Gilbert Syndrome
- E80.5 Crigler-Najjar Syndrome
- E80.6 Other Disorders of Bilirubin Metabolism
- E80.7 Disorders of Bilirubin Metabolism, Unspecified

Acute Intermittent Porphyria (E80.2)
ALA Synthase Inhibition

ORPHAN DRUG ACT OF 1983

Year of Approval

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Progression of Orphan Therapeutics
Metabolic Disorders (E70-E90)
Disorders of Mineral Metabolism (E83)

Older Drugs for Disorders of Mineral Metabolism
Penicillamine
Cuprimine (1970)
Depen (1978)

E83.0 Disorders of Copper Metabolism
E83.1 Disorders of Iron Metabolism
E83.2 Disorders of Zinc Metabolism
E83.3 Disorders of Phosphorus
Metabolism and Phosphatases
E83.4 Disorders of Magnesium
Metabolism
E83.5 Disorders of Calcium Metabolism
E83.8 Other Disorders of Mineral Metabolism
E83.9 Disorders of Mineral Metabolism, Unspecified

**Wilson Disease (E83.0)**
Copper Chelation; Copper Absorption Inhibition

**Hemosiderosis (E83.1)**
Iron Chelation

**Hypercalcemia (E83.5)**
Calcium Resorption Inhibition; Calcimimetic Agent

**Syrpine**

**Didronel**

**Galzin**

**Galzin**

**Sensipar**

**Zemplar**

**Ferriprox**

**Sensipar**

**Exjade**

**Zometa**

**Zabel**

**Sensipar**

**Ferriprox**

**Sensipar**

**Sensipar**

**Xgeva**

**ORPHAN DRUG ACT OF 1983**

Year of Approval

Progression of Orphan Therapeutics
Metabolic Disorders (E70-E90)
Amyloidosis (E85) (Excluding Alzheimer Disease)

Older Drugs for Amyloidosis
n/a

E85.0 Non-Neuropathic Heredofamilial Amyloidosis
E85.1 Neuropathic Heredofamilial Amyloidosis
E85.2 Heredofamilial Amyloidosis, Unspecified
E85.3 Secondary Systemic Amyloidosis
E85.4 Organ-Limited Amyloidosis
E85.8 Other Amyloidosis
E85.9 Amyloidosis, Unspecified

Familial Mediterranean Fever (E85.0)
Microtubule Polymerization Inhibition

ORPHAN DRUG ACT OF 1983

Year of Approval
Progression of Orphan Therapeutics
Metabolic Disorders (E70-E90)
Other Metabolic Disorders (E88)

Older Drugs for Other Metabolic Disorders
n/a

E88.0 Disorders of Plasma Protein Metabolism, Not Elsewhere Classified
E88.1 Lipodystrophy, Not Elsewhere Classified
E88.2 Lipomatosis, Not Elsewhere Classified
E88.3 Tumour Lysis Syndrome
E88.8 Other Specified Metabolic Disorders
E88.9 Metabolic Disorders, Unspecified

Lipodystrophy (E88.1)
Leptin Analog (Replacement)

ORPHAN DRUG ACT OF 1983
Number of Approved Orphan Drugs per Individual Rare Metabolic Disorders

- Gaucher Disease Type I (E75.2)
- Pompe Disease (E72.2)
- Cystinosis (E72.0)
- Cystic Fibrosis (E83.1)
- Phenylketonuria Type I (E70.2)
- Tyrosinemia Type I (E71.1)
- Cystinuria (E72.0)
- Homocystinuria (E72.1)
- Fabry Disease (E75.2)
- Hunter Syndrome (E76.1)
- Maroteaux-Lamy Syndrome (E76.2)
- Morquio A Syndrome (E80.2)
- Acute Intermittent Porphyria (E85.4)
- Cystic Fibrosis (E85.5)
- Familial Mediterranean Fever (E85.1)
- Homozygous Familial Hypercholesterolemia (E74.0)
- Hemosiderosis (E78.0)
- Primary Systemic Carnitine Deficiency (E71.3)
- Hurler Syndrome (E72.0)
- Hurler-Scheie Syndrome (E72.0)
- Congenital Sucrese-Isomaltase Deficiency (E76.0)
- Gaucher Disease Type II (E73.1)
- Gaucher Disease Type III (E73.5)
- Hyperparathyroidism (E74.0)
- Hypercholesterolemia (E72.0)
Length of Registration Interest per Individual Rare Metabolic Disorders

- Hypercalcemia (E83.5)
- Cystinosis (E72.0)
- Gaucher Disease Type I (E74.2)
- Hyperammonemia (E84.0)
- Cystic Fibrosis (E83.1)
- Hemosiderosis (E83.1)
- Wilson Disease (E78.0)
- Phenyketonuria Type I (E70.0)
- Tyrosinemia Type I (E70.2)
- Primary Systemic Carnitine Deficiency (E71.3)
- Congenital Sucrease-Isomaltase Deficiency (E73.0)
- Hurler & Hurler-Scheie Syndrome (MPS I) (E76.0)
- Morquio A Syndrome (MPS IV A) (E76.1)
- Hunter Syndrome (MPS II) (E76.2)
- Maroteaux-Lamy Syndrome (MPS VII) (E76.2)
- Acute Intermittent Porphyria (E80.2)
- Cystic Fibrosis (E84.9)
- Familial Mediterranean Fever (E85.5)
- Lipodystrophy (E88.1)
**Comments**

*A Few Observations* – This report on the *Progression of Orphan Therapeutics: Metabolic Disorders* has provided visual displays of orphan drug approvals for twelve rare Metabolic Disorder categories. While it is not the intent here to provide any comprehensive assessment of the findings, a few general observations are as follows:

*Rare Diseases Classification System* – This report used the *ICD-10 Version: 2015* system, but as noted above it’s not optimized with respect to orphan drugs or rare diseases, although so far it appears to work reasonable well for rare Metabolic Disorders.

*Mechanisms of Action of Approved Orphan Drugs for Rare Metabolic Disorders* – As is evident from the graphs for the twelve Metabolic Disorders on pages 7-18, these orphan drugs have a variety of mechanisms of action. Of note is that enzyme replacement is involved in 14 of the 45 approved orphan drugs, or 31.1%. Another common mechanism involves enzyme inhibition.

*Number of Approved Orphan Drugs per Individual Rare Metabolic Disorder* – As shown in the graph on page 19, these vary considerably, highest for Gaucher Disease (6), Hypercalcemia (6), Hyperammonemia (5), and Cystinosis (3), followed by four disorders with 2 each; the rest has 1 each.

*Lengths of Registration Interests* – As shown in the graph on page 20, these vary significantly, highest for Hypercalcemia (27.58 decimal years), Cystinosis (24.66 years), Gaucher Disease (23.33 years), and Hyperammonemia (23.08 years), but the great majority of orphan drug approvals for individual rare Metabolic Disorders occurred within the same year.
Applications and Benefits – There are numerous applications and benefits associated with having in a single place high-level data and info-graphics of approved orphan drugs for individual rare disease categories, sorted by their dates of approval, including:

• **Enabling** visual examinations of changes over time in registration activities for individual rare diseases, such as the number and identity of the approved orphan drugs and their years of approval, the number of approved orphan drugs per individual rare diseases, and the duration of registration activities involving individual rare diseases.

• **Relating** registration activities across different rare diseases to unmet medical need, and thus, helping to prioritize drug discovery and development needs.

• **Providing** background information for assessing patient therapeutic response characteristics of approved orphan drugs and for other projects.

• **Serving** educational objectives of pharmacology, translational medicine and therapeutics, drug discovery and development, by providing perspectives regarding the progression of modern therapeutics.

Future work on this project on the *Progression of Orphan Therapeutics* will include addressing other rare disease categories; examining different mechanisms of action; and generating lists of both proprietary and established names of approved drugs.
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a) to conduct scientific assessments of characteristics of drug treatments of human diseases based on available information and relevant frameworks;
b) to analyze and report such findings by indications and therapeutic areas, pharmacological mechanisms, types of endpoints, and disease types;
c) to co-sponsor seminars, particularly in the Greater Philadelphia region, directed at the pharmaceutical startup community, exploring lessons from the findings; and
d) to engage in other activities related to the objectives of the corporation, that will further its mission.

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