Investigating How Orphan Drug Manufacturers Can Optimize Clinical Trial Design So Patients Across Geographies Can Access Life-Saving Innovations

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BACKGROUND AND OBJECTIVES

- Orphan drugs offer significant clinical benefits; however, their cost leads to potentially unsustainable budget impact.
- In the case of non-orphan drugs United States (US) Managed Care Organizations (MCOs) and Pharmacy Benefit Managers (PBMs) often provide coverage, regardless of price and limitations of data at launch, whereas European payers tend to review data more critically before providing coverage. However, the considerations may be different for rare and orphan drugs.
- This poses a challenge to manufacturers of how to design clinical trials that ensure their product will be reimbursed across geographies.

METHODOLOGY

PRODUCT INCLUSION CRITERIA:

- Various publicly available lists of the most expensive drugs were reviewed, and the most appropriate list was selected. This research was completed in early 2022 so the list selected reflects the most expensive drugs in the US as of the year-end 2021.
- Prices published in the list were cross-checked on PriceRx and the final list of drugs for analysis was developed.
- All drugs included in the analysis were indicated in a population with a prevalence of fewer than 200,000 patients in the US, to meet the definition of a rare disease as defined by the US Food and Drug Administration (FDA) or were listed by the National Organization for Rare Disorders (NORD).
- In order to be included in the analysis, drugs had to be oral or subcutaneous self-administered products.
- Products administered by a physician and reimbursed under the medical benefit, including cell and gene therapies, were excluded from this analysis in order to narrow the focus to drugs covered under the pharmacy benefit where US payers have the same management tools at their disposal.

SECONDARY RESEARCH (UNITED STATES, FRANCE, GERMANY, UNITED KINGDOM):

- In the US, France, Germany, and the United Kingdom (UK), public sources were used to determine the list price of each product.
- In the US, secondary sources were used to determine formulary status for each of the 10 drugs for the three major payers in the US: Aetna/CVS, Cigna/ESI, and UHC/Optum.
- In France, Transparency Committee (TC) reports were reviewed for each of the 10 drugs.
- In Germany, Federal Joint Committee / Gemeinsamer Bundesausschuss (GBA) reports were reviewed for each drug.
- In the UK, National Institute for Health and Care Excellence (NICE) assessments were reviewed for each drug.

QUANTITATIVE PRIMARY RESEARCH (UNITED STATES ONLY):

- N=24 payers representing 116 million covered lives responded to a survey.
- The survey included questions about trial design consideration for rare and orphan drugs, including questions about acceptability of placebo comparators, shorter trial durations, smaller trial sizes, open-label extension data, and data gaps at launch and how these factors impact US payor management.

QUALITATIVE PRIMARY RESEARCH (UNITED STATES, FRANCE, GERMANY, UNITED KINGDOM):

- N=4 payers (one per market) in national decision-making roles were interviewed through one-hour in-depth telephone interviews (IDIs).
- During the interviews, the market access decisions for the 10 drugs, as well as the rationale for these decisions, was discussed.
- Respondents were probed on the impact of the comparator, trial duration, trial size, open-label extension data, and data gaps at launch and their importance in decision-making for rare and orphan drugs.

CONCLUSIONS

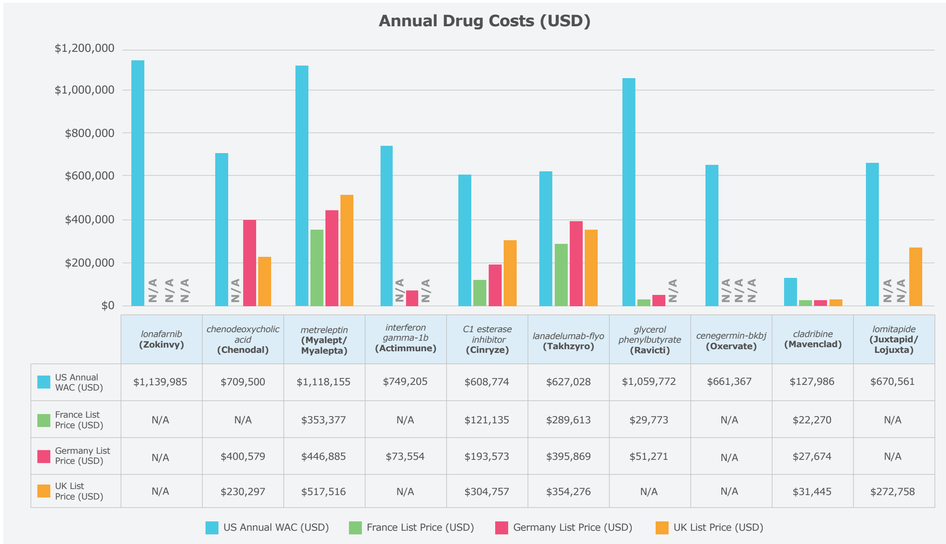
- Across the markets analyzed, payers most often provide moderate to restrictive access to rare and orphan drugs.
  - This is in contrast to other disease areas where there is more open access in the US compared with European markets. In the case of rare and orphan diseases, US payers have similar requirements and coverage criteria to their European counterparts.
- Payers prefer to see clinical trial duration of at least 6 months, especially in the US and France. However, there have been cases where rare and orphan drugs have obtained at least moderate access with shorter durations. Manufacturers should design trials as long as possible but may balance the urgent need for treatments and consider that reimbursement may be possible with shorter trials.
- Smaller trial sizes are not a concern for most payers as they understand that because of the smaller patient populations characteristic of rare diseases, larger trials may be unrealistic.
- Even though US payers are not concerned with placebo comparators, manufacturers should consider the drawbacks of placebo-controlled trials. This should be balanced with the challenges associated with active comparator trials, especially in scenarios where there are no existing treatment options. Manufacturers may face criticism from the TC and GBA if these bodies do not agree with the choice of comparator. Despite this criticism, patients will most likely still have access to these markets, but the manufacturer may have to accept a lower price.
- Open-label extension data are highly valued in the US and the UK, therefore these data are important to develop, even though they will not be valued in France or even considered by German payers.

RESULTS

Top 10 Self-Administered Pharmacy Drugs by US WAC as of Year-End 2021 (Listed by Prevalence, Lowest to Highest)

Drug	Route of Administration	Indication	Estimated Number of Patients in the US
lonafarnib **Zokinvy**	Oral (capsules)	• Hutchinson-Gilford progeria syndrome • Progeroid laminopathies	17 *[Hutchinson-Gilford progeria syndrome]*
chenodeoxycholic acid **Chenodal**	Oral (tablets)	• Cerebrotendinous xanthomatosis • Radiolucent gallstones	272 *[Cerebrotendinous xanthomatosis]*
metreleptin **Myalept/Myalepta**	Injection (subcutaneous), self-administered	• Leptin deficiency in patients with congenital or acquired generalized lipodystrophy	332
interferon gamma-1b **Actimmune**	Injection (subcutaneous), self-administered	• Reducing frequency and severity of infections associated with chronic granulomatous disease (CGD) • Delaying time to disease progression in patients with severe malignant osteopetrosis (SMO)	1,329 *[Chronic granulomatous disease]*
C1 esterase inhibitor [human] **Cinryze**	IV* (self-administered)	• Angioedema (adults) • Hereditary angioedema (pediatric)	3,324 *[Hereditary angioedema]*
lanadelumab-flyo **Takhzyro**	Injection (subcutaneous), self-administered	• Prophylaxis to prevent attacks of hereditary angioedema (HAE)	6,648
glycerol phenylbutyrate **Ravicti**	Oral (liquid)	• High blood levels of ammonia caused by urea cycle disorder	9,497
cenegermin-bkbj **Oxervate**	Ophthalmic solution for topical ophthalmic use	• Neurotrophic keratitis	166,202
cadribine **Mavenclad**	Oral (tablets)	• Relapsing forms of multiple sclerosis (MS)	255,000**
lomitapide **Juxtapid/Lojuxta**	Oral (capsules)	• Homozygous familial hypercholesterolemia	1.3 million**

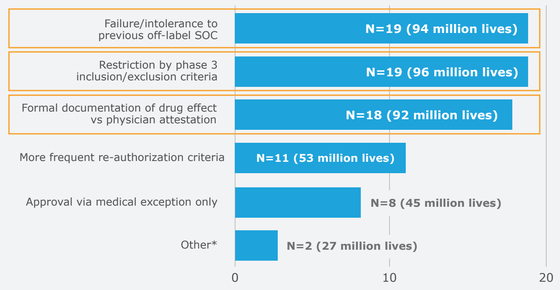
*The Mix2Vial® transfer device is a needle-free reconstitution and transfer system to facilitate reconstitution and administration. It can be self-administered by the patient or administrated by a caregiver or healthcare professional.
**Although both cladribine and lomitapide have a prevalence >200K in the US, both are listed in the National National Organization for Rare Disorders and therefore were considered rare for this analysis.



	lonafarnib (Zokinvy)	chenodeoxycholic acid (Chenodal)	metreleptin (Myalept/ Myalepta)	interferon gamma-1b (Actimmune)	C1 esterase inhibitor (Cinryze)	lanadelumab-flyo (Takhzyro)	glycerol phenylbutyrate (Ravicti)	cenegermin-bkbj (Oxervate)	cladribine (Mavenclad)	lomitapide (Juxtapid/ Lojuxta)
US Annual WAC (USD)	$1,139,985	$709,500	$1,118,155	$749,205	$608,774	$627,028	$1,059,772	$661,367	$127,986	$670,561
France List Price (USD)	N/A	N/A	$353,377	N/A	$121,135	$289,613	$29,773	N/A	$22,270	N/A
Germany List Price (USD)	N/A	$400,579	$446,885	$73,554	$193,573	$395,869	$51,271	N/A	$27,674	N/A
UK List Price (USD)	N/A	$230,297	$517,516	N/A	$304,757	$354,276	N/A	N/A	$31,445	$272,758

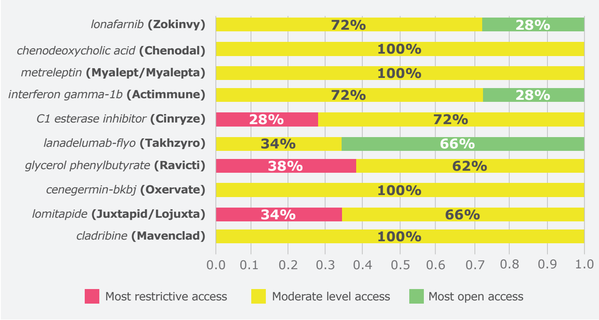
MANAGEMENT OF RARE AND ORPHAN DRUGS: US

Management tools used for rare and orphan drugs
(by number of mentions, N=24 payers (116 million lives))



*Other: Center of Excellence Network (Maximizer / Accumulator), Evidence Based Guidelines + Restrict to Specialists.

US formulary access for top 10 pharmacy benefit drugs in the United States (by WAC) at top 3 US payer organizations



UNITED STATES

- In the US, decisions are made based on clinical need and efficacy relative to current standard of care, if any exists.
- US payers restrict utilization of costly rare and orphan drugs to the specialty tier, often with prior authorizations. In some cases, these drugs are only available through medical exception.
- Failure/intolerance of previous off-label standard of care, restrictions by phase 3 trial inclusion/exclusion criteria, and formal documentation of drug effect vs physician attestation are common utilization management tools used by US payers.

MANAGEMENT OF RARE AND ORPHAN DRUGS: FRANCE, GERMANY, AND UNITED KINGDOM

Drug	France	Germany	United Kingdom
lonafarnib **Zokinvy**	Temporary use authorization	Under assessment	Not yet reviewed
chenodeoxycholic acid **Chenodal**	Not reimbursed	Non-quantifiable added benefit	NHS England and NICE have not issued any guidelines or policies on managing CTX with chenodeoxycholic acid
metreleptin **Myalept/Myalepta**	**ASMR IV** (generalized lipodystrophy); **ASMR V** (partial lipodystrophy)	Non-quantifiable added benefit	Recommend, simple discount
interferon gamma-1b **Actimmune**	Non reimbursable	Non-quantifiable added benefit	Not recommended
C1 esterase inhibitor [human] **Cinryze**	**ASMR V** (No superiority vs Berinert which received ASMR III)	Non-quantifiable added benefit	Licensed for long-term prophylaxis of patients 6 years and older with HAE types 1 and 2 in the UK
lanadelumab-flyo **Takhzyro**	**ASMR IV** (Only for severe patients over 12 years resistant to oral treatment)	No added benefit	Recommended with commercial agreement
glycerol phenylbutyrate **Ravicti**	**ASMR V** (vs Ammonaps which received an ASMR I)	Non-quantifiable added benefit	Recommended by NHS Scotland only
cenegermin-bkbj **Oxervate**	**ASMR IV** (Only data vs placebo with a weak magnitude of effect)	Non-quantifiable added benefit	Withdrawn / not recommended
cladribine **Mavenclad**	**ASMR V** (No superiority / no added benefit vs other MS treatments)	No added benefit	Recommended
lomitapide **Juxtapid/Lojuxta**	**ASMR IV** (Only for homozygote)	No added benefit	Authorized for use as an adjunct to a low-fat diet and other lipid-lowering medicinal products with or without low-density lipoprotein apheresis in adult patients with homozygous familial hypercholesterolemia

Highest recommendation | Mid-level or restricted recommendations | Not recommended

FRANCE

- All drugs included in this analysis are determined by the TC to have a minor or no clinical added value (ASMR IV or ASMR V) that limits price potential.
- In cases of ASMR V, the drug can only be listed if it has a lower price than comparators or provides cost savings.
- In cases of ASMR IV, there is a possibility for a higher price vs comparators, but it will be limited.

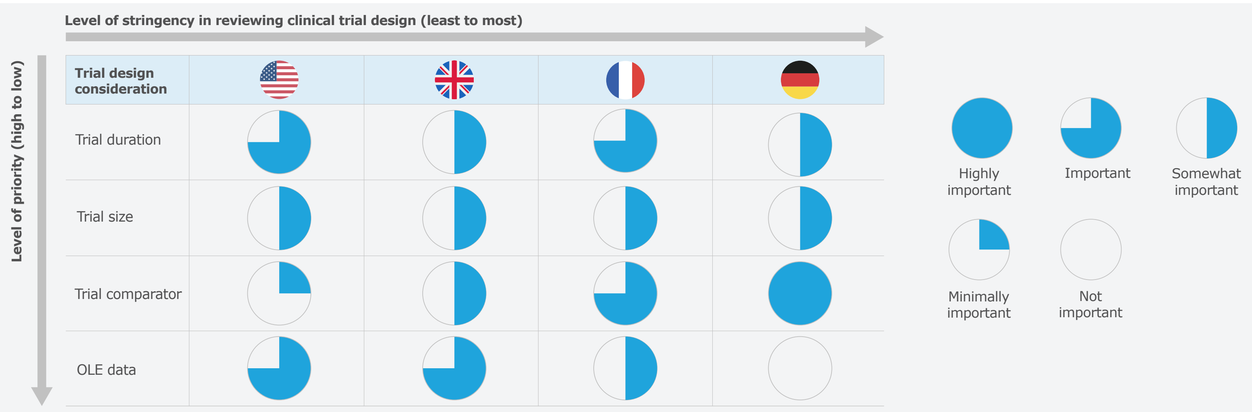
GERMANY

- Orphan drugs are different from non-orphan drugs in that they are exempt from the regular assessment process in Germany and all products receive at least a non-quantifiable added benefit, regardless of the evidence available.
- The regular benefit assessment is not conducted until the drug exceeds an annual revenue of €50 million. When this threshold is exceeded, a comparative assessment is conducted. At this time, lack of a comparator is likely to negatively impact the added benefit rating.
- Historically, >50% of orphan drugs are determined to have an added benefit that is not proven (or no added benefit).
- However, in many cases, years may pass before the threshold is exceeded and the regular assessment is conducted, and in some cases, the threshold is never reached.
- There is a new draft bill that would lower this threshold to €20 million per year.

UNITED KINGDOM

- Six of the drugs analyzed are recommended in the UK; many others have not been given a formal recommendation or are not recommended in this market.

Trial design considerations for rare and orphan drugs in the United States, Germany, France, and the United Kingdom



TRIAL DURATION

- **US:** Trial duration is not a formal criterion, but US payers prefer to see longer trial durations compared with their European counterparts. 20 of 24 payers only view trial duration of >12 months to be acceptable, with four of 21 payers looking for trial durations of more than two years.
- **France:** In France, payers prefer two years of trial duration; however, in certain disease states, especially those with rapid disease progression, a trial duration of six months to a year, or sometimes even less, is considered acceptable. Acceptable trial duration is largely based on clinician input. The French payor interviewed suggested that manufacturers provide interim analysis for initial coverage and then discuss again after longer-term data become available.
- **Germany:** Trial duration is a formal criterion but ultimately will not affect the benefit rating unless the €50 million threshold is exceeded. Still, the German payor interviewed stated a preference for a minimum of six months trial duration unaided during the IDI.
- **UK:** Trial duration is a formal criterion and NICE requires a duration of at least six months. The UK payor interviewed stated a need for a minimum of six months trial duration unaided during the IDI.

TRIAL SIZE

- **US:** Trial size is not a formal criterion and US payers are only moderately concerned with smaller sample sizes for rare and orphan drugs, given limited patient numbers.
- **France:** French payers are not concerned with smaller trials for rare and orphan drugs. They realize that the size of the population is related to the magnitude of the difference observed, especially if duration is sufficient. Spinal Muscular Atrophy was cited as an example where the sample size was 12 per treatment arm and 12 out of 12 patients responded to treatment leading to an ASMR II.
- **Germany:** The size of the trial is not a formal criterion; however, the p-value is. German payers are significantly concerned with smaller trial sizes for rare and orphan drugs but are still required to give at least a non-quantifiable added benefit rating.
- **UK:** Trial size is not a formal criterion and payers in the UK are only moderately concerned with smaller trials because they can use natural history and other data to satisfy models and increase their confidence in a product's efficacy.

TRIAL COMPARATOR

- **US:** Trial comparators are not a formal criterion used in US P&T review process. 21 of 24 payers accept placebo comparators. Placebo comparators are considered appropriate in cases where there is no treatment alternative or in last line of therapy.
- **France:** Trial comparators are a formal criterion used in the TC review process and in cases where there is no comparator, indirect comparisons will be accepted, based on clinician input. If there is no treatment or very weak treatments are available, a placebo comparator will be accepted. However, if specialists currently are using other products as the standard of care, head-to-head data will be required.
- **Germany:** Trial comparators are a formal criterion used in the GBA review, but even drugs with placebo comparators receive a non-quantifiable added benefit until the €50 million threshold is exceeded. Placebo comparators may be considered appropriate in cases where there is no treatment alternative or in last line therapies.
- **UK:** Trial comparators are a formal criterion in the NICE review process. This is because the process is inherently comparative and requires comparative decision-making. In cases of a placebo comparator, NICE will accept indirect comparisons, and "do nothing" or "best supportive care" can be considered an appropriate comparator.

OLE DATA

- **US:** Open-label extension data are valued by US payers and 21 of 24 payers consider open-label extension data in their formulary management. Since US formulary decisions are made annually, it is possible that additional data may lead to better formulary placement (although any changes are most likely to occur as a result of price discounts).
- **France:** Open-label extension data are typically not deemed appropriate and do not often impact the market access decision.
- **Germany:** Open-label extension data are not considered by German payers because these are seen as biased.
- **UK:** Open-label extension data are valued and may lead to an improved review, even after the initial decision has been made.

SOURCES

1.Medispan. (2022). PriceRx. Retrieved September 2022; 2.CGM. (2022). Lauer Taxe. Retrieved September 2022; 3. Theriaque. (2017). Database of medicines Theriac. Retrieved September 2022 ; 4.MIMS. (2017). MIMS Pricing. Retrieved September 2022; 5. National Organization for Rare Disorders. (2021). Retrieved September 2022; 5a. Hutchinson-Gilford Progeria Syndrome; 5b. Congenital Generalized Lipodystrophy; 5c. Multiple Sclerosis ; 5d.Chronic Granulomatous Disease; 5e. Familiar Hypercholesterolemia; 5f. Hereditary Angioedema; 6. Food and Drug Administration. (2020). Zokinvy FDA Label. Retrieved September 202; 7.Food and Drug Administration. (2014). Myalept FDA Label. Retrieved September 2022; 8. Food and Drug Administration. (2019). Mavencald FDA Label. Retrieved September 2022; 9. Food and Drug Administration. (2017). Ravicti FDA Label. Retrieved September 2022; 10. Food and Drug Administration. (2021). Actimmune FDA Label. Retrieved September 2022; 11. Food and Drug Administration. (2019). Oxervate FDA Label. Retrieved September 2022; 12. Food and Drug Administration. (2012). Juxtapid FDA Label. Retrieved September 2022; 13. Food and Drug Administration. (2022). Cinryze FDA Label. Retrieved September 2022; 14. American Association for Clinical Chemistry. (2019) Inherited Disorders of the Urea Cycle. Retrieved September 2022; 15. Biologics: Targets and Therapy. (2013). Hereditary angioedema: epidemiology, management, and role of icatibant. Retrieved September 2022; 16. National Library of Medicine. (2022). Neurotrophic Keratitis. Retrieved September 2022; 17. Travere Therapeutics. (2022). Chenodeoxycholic Acid. Retrieved September 2022; 18. Body Surface Area Calculator. (2022). Retrieved September 2022; 19. American Journal of Medical Genetics. (2006). Hutchinson–Gilford progeria syndrome: Review of the phenotype. Retrieved September 2022; 20. NICE (2022). National Institute for Health and Care Excellence. Retrieved September 2022; 20a. Lonafarnib for treating progeria and progeroid laminopathies; 20b. Cladribine for treating relapsing–remitting multiple sclerosis; 20c. Cenegermin for treating neurotrophic keratitis; 20d. Lanadelumab for preventing recurrent attacks of hereditary angioedema; 20e. Ibrutinib for treating relapsed or refractory mantle cell lymphoma; 20f. Metreleptin for treating lipodystrophy; 20g. Lanadelumab for preventing recurrent attacks of hereditary angioedema; 20h. Clinical evidence review of lomitapide for treating homozygous familial hypercholesterolemia in adults; 20i. Clinical evidence review of chenodeoxycholic acid for treating cerebrotendinous xanthomatosis; 21. NHS. (2022). Specialty Pharmacy Service. Metreleptin. Retrieved September 2022; 22. Pharmaceutical Technology. (2018). Retrieved September 2022. 22a. Comparing the US's ten most expensive drugs with prices in the UK; 22b. NICE rejects funding for Dompé's rare eye disease drug; 23. Ministry of Social Affairs and Health. (2022). Economic Committee for Health Products (CEPS). Myalepta. Retrieved September 2022; 24. Aetna. (2022). 2022 Drug Search for Aetna Standard Plan. Retrieved September 2022; 25. Aetna. (2021). Aetna Specialty Pharmacy Clinical Policy Bulletins Non-Medicare Prescription Drug Plan. Retrieved September 2022; 26. Aetna. (2022). Clinical Policy Bulletins. Retrieved September 2022; 26a. Interferons; 26b. Hereditary Angioedema; 27. Aetna. (2021). 2021 Aetna Pharmacy Drug Guide. Advanced Control Plan. Retrieved September 2022; 28. Cigna. (2022). Cigna National Formulary Coverage Policy. Retrieved September 2022; 28a. PA Zokinvy; 28b. PA Lipodystrophy – Myalept; 28c. PA Multiple Sclerosis – Mavenclad; 28d. PA Metabolic Disorders – Phenylbutyrate Products; 28e. PA Interferon – Actimmune; 28f. PA Ophthalmology – Oxervate; 28g. PA Hereditary Angioedema – Takhzyro; 28h. PA Homozygous Familial Hypercholesterolemia – Juxtapid; 28i. PA Hereditary Angioedema - C1 Esterase Inhibitors; 28j: PA Chenodal; 29. Cigna. (2022). Cigna Performance 3-Tier Prescription Drug List. Retrieved September 2022; 30. Cigna. (2022). 2022 Cigna Drug Lists for Plans Offered by Employers. Retrieved September 2022; 31. United Healthcare. (2022). 2022 Prescription Drug List. Retrieved September 2022; 32. United Healthcare. (2022). UnitedHealthcare Pharmacy. Retrieved September 2022; 32a. Zokinvy Prior Authorization; 32b. Myalept Prior Authorization; 32c. Mavenclad Prior Authorization; 32d. Ravicti Prior Authorization; 32e. Actimmune Prior Authorization; 32f. Oxervate Prior Authorization; 32g. Takhzyro Prior Authorization; 32h. Juxtapid Prior Authorization; 32i. Cinryze Prior Authorization; 32j. Chenodal Prior Authorization; 33. United Healthcare. (2022). Your 2022 Prescription Drug List. Traditional 3-Tier. Retrieved September 2022; 34. United Healthcare. (2022). Complete Drug List (Formulary) 2022. HealthSelect℠ Medicare Rx (PDP). Retrieved September 2022; 35. MIMIT. (2022). Formulary LookUp. Retrieved September 2022; 36. Endocrine. (2022). Long-term effectiveness and safety of metreleptin in the treatment of patients with generalized lipodystrophy. Retrieved September 2022; 37. Clinicaltrials.gov. (2022). Retrieved September 2022; 37a. A Safety and Efficacy Study of Oral Cladribine in Subjects With Relapsing-remitting Multiple Sclerosis (RRMS) (CLARITY); 37b. Efficacy and Safety of HPN-100 for the Treatment of Adults With Urea Cycle Disorders; 37c. Efficacy and Safety Study of DX-2930 to Prevent Acute Angioedema Attacks in Patients With Type I and Type II HAE; 37d. A Safety and Efficacy Study of AEGR-733 to Treat Homozygous Familial Hypercholesterolemia (FH); 37e. Safety and Efficacy of CDCA in CTX Chenodeoxycholic Acid (CDCA) in Patients Affected by Cerebrotendinous Xanthomatosis (CTX); 38. Scottish Medicines Consortium. (2018). Glycerol Phenylbutyrate (Ravicti). Retrieved September 2022; 39. The Federal Joint Committee (Gemeinsamer Bundesausschuss). (2022). Retrieved September 2022; 39a. Metreleptin; 39b. Cladribin; 39c. Glycerolphenylbutyrat; 39d. Cenegermin; 39e. Lanadelumab; 39f. Lomitapid; 40. IQWiG. (2018). Retrieved September 2022; 40a. Cladribine (multiple sclerosis) - Benefit assessment; 40b. Glycerol phenylbutyrate (urea cycle disorders) – assessment; 40c. Metreleptin (lipodystrophy) - assessment; 40d. Lanadelumab in hereditary angioedema: added benefit not proven; 41. Eiger Biopharmaceuticals. (2021). Third Quarter 2021 Financial Results and Provides Business Update. Retrieved September 2022; 42. Haute Autorité de Santé (HAS). (2019). Transparency Committee Opinion Summary. Retrieved September 2022; 42a. Myalepta; 42b. Mavecla; 42c. Ravicti; 42d. Oxervate; 42e. Takhzyro; 42f. Juxtapid; 42g. Cinryze; 42h. Chenodal; 43. ViDAL. (2022). IMUKIN 2 x10 6 IU (0.1 mg) sol inj. Retrieved September 2022; 44. FDA. (2022). Rare Diseases at FDA. Retrieved October 2022.

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