Orphan Medicines in Europe
Are they really breaking the bank?

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The headlines we’ve all become accustomed to around orphan medicines

List prices are regularly quoted without managed access arrangements or note of confidential discounts

US perspectives have recently increased their focus on high costs in light recent events, rather than budget impact
Orphan Medicines in Europe - Will They Really Break the Bank?

1. Uptake Trends for Orphan Medicines in Europe

2. Orphan Medicines in a Wider Budgetary and Uptake Context

3. Payer Moves to Collaborative Negotiations on Price
Spending on Specialty medicines has risen rapidly, growing faster than the total market

*After the Hep C bubble, the European pharma growth rate dips to 4%*

- After the ”HepC bubble”, the growth rate is down in low single digits in Europe
- Traditional medicine has very low value growth – but a sustained volume growth
- Specialty, consisting of several segments, shows a sustained growth

Source: IQVIA MIDAS MAT Q3 2017; Recent Hep C launches included: SOVALDI, HARVONI, VIEKIRAX, DAKLINZA, EPCLUSA, EXVIERA, PEGASYS, SOVRIAD, COPEGUS, ZEPATIER
Orphan medicines approvals in Europe have risen substantially since 2000 legislation

Number of total authorised medicines, and authorised orphan medicines

Source: EMA 2018
Oncology orphan medicines constitute 37% of all orphans and 53% of European Orphan medicines sales in 2018

**Number of Orphan drugs**

- Oncologics: 37%
- Other: 16%
- Other Alimentary Tract And Metabolism Products: 12%
- Blood Coagulation: 6%
- Other Cns: 4%
- Other Cardiovasculars: 3%
- Immunosuppressants: 3%
- All Other Respiratory: 6%
- Hematopoietic Growth Factors: 6%
- Antituberculars: 3%
- Other: 3%
- Antituberculars: 3%
- Other: 6%
- Other: 8%
- Other: 8%
- Other: 6%
- Other: 8%
- Other: 14%
- Other: 53%

**European Orphan drugs sales, 2018**

- Oncologics: 53%
- Other: 14%
- Other: 8%
- Other: 8%
- Other: 6%
- Other: 6%
- Other: 5%
- Other: 6%
- Other: 8%
- Other: 3%
- Other: 6%
- Other: 3%
- Other: 3%
- Other: 6%
- Other: 3%
- Other: 6%
- Other: 8%
- Other: 8%
- Other: 14%
- Other: 53%

**Limitations:** IQVIA MIDAS coverage may be subject to limitations where volumes are low or distributed through limited wholesaler or pharmacy networks and some product sales may be understated for lower volume products, which could include orphan drugs.

Source: IQVIA MIDAS MAT March 2018

Notes: All products included in number of product chart, only ones with sales data included in sales chart
Orphan availability vs New Active Substance (NAS) availability varies on a country level

Source: IQVIA European Thought Leadership
In 2016, 3.5% total pharma list price spend in Europe was on authorised Orphan drugs, ~ €6.4Bn

Key Observations:

- Of the €4.8Bn in spending increase in 2016 in Europe, Orphan drugs contributed 6.6% of growth.

- Orphan drugs are a relatively small part of the drug budget in any country

- 4 countries showing the highest orphan drug contribution to growth: Denmark, Belgium, Ireland and Slovenia

- Countries where the Orphan Drugs sales is >= 4% of the total country sales in 2016: Germany, Slovenia and UK

<table>
<thead>
<tr>
<th>Country</th>
<th>Orphan Drug Sales 2016, €Mn</th>
<th>%MS of Orphan Drug sales 2016</th>
<th>Orphan Drugs Contribution to growth 2015-2016, LC€</th>
</tr>
</thead>
<tbody>
<tr>
<td>GERMANY</td>
<td>1,717.6</td>
<td>4.3%</td>
<td>9.4%</td>
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<tr>
<td>FRANCE</td>
<td>1,077.0</td>
<td>3.8%</td>
<td>4.9%</td>
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<tr>
<td>ITALY</td>
<td>876.6</td>
<td>3.4%</td>
<td>2.6%</td>
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<td>UK</td>
<td>857.4</td>
<td>4.0%</td>
<td>9.1%</td>
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<td>SPAIN</td>
<td>617.0</td>
<td>3.2%</td>
<td>10.2%</td>
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<tr>
<td>BELGIUM</td>
<td>176.5</td>
<td>3.7%</td>
<td>38.7%</td>
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<tr>
<td>NETHERLANDS</td>
<td>155.6</td>
<td>3.2%</td>
<td>7.3%</td>
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<tr>
<td>SWEDEN</td>
<td>132.2</td>
<td>3.8%</td>
<td>9.0%</td>
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<td>PORTUGAL</td>
<td>104.2</td>
<td>3.1%</td>
<td>-5.1%</td>
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<td>AUSTRIA</td>
<td>103.3</td>
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<td>7.1%</td>
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<td>DENMARK</td>
<td>86.3</td>
<td>3.7%</td>
<td>16.8%</td>
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<tr>
<td>IRELAND</td>
<td>63.8</td>
<td>3.2%</td>
<td>14.6%</td>
</tr>
<tr>
<td>NORWAY</td>
<td>62.4</td>
<td>3.6%</td>
<td>11.1%</td>
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<tr>
<td>POLAND</td>
<td>58.4</td>
<td>1.0%</td>
<td>-1.0%</td>
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<tr>
<td>HUNGARY</td>
<td>49.7</td>
<td>2.2%</td>
<td>7.5%</td>
</tr>
<tr>
<td>FINLAND</td>
<td>49.5</td>
<td>2.2%</td>
<td>6.8%</td>
</tr>
<tr>
<td>SLOVAKIA</td>
<td>41.4</td>
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<td>6.8%</td>
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<tr>
<td>CZECH REPUBLIC</td>
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<td>10.0%</td>
</tr>
<tr>
<td>ROMANIA</td>
<td>33.5</td>
<td>1.3%</td>
<td>0.1%</td>
</tr>
<tr>
<td>BULGARIA</td>
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<td>2.2%</td>
<td>-7.0%</td>
</tr>
<tr>
<td>SLOVENIA</td>
<td>23.1</td>
<td>4.1%</td>
<td>13.2%</td>
</tr>
<tr>
<td>CROATIA</td>
<td>14.5</td>
<td>2.2%</td>
<td>1.0%</td>
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<tr>
<td>LITHUANIA</td>
<td>6.0</td>
<td>1.1%</td>
<td>-4.3%</td>
</tr>
<tr>
<td>ESTONIA*</td>
<td>4.1</td>
<td>1.8%</td>
<td>1.5%</td>
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<tr>
<td>LATVIA*</td>
<td>1.2</td>
<td>0.4%</td>
<td>-1.0%</td>
</tr>
<tr>
<td>GREECE*</td>
<td>0.6</td>
<td>0.0%</td>
<td>-6.3%</td>
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<th>Country</th>
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<th>%MS of Orphan Drug Sales 2016</th>
<th>Orphan Drugs Contribution to growth 2015-2016, LC€</th>
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<tbody>
<tr>
<td>Total Europe</td>
<td>6,376.5</td>
<td>3.5%</td>
<td>6.6%</td>
</tr>
</tbody>
</table>

Limitations: IQVIA MIDAS coverage may be subject to limitations where volumes are low or distributed through limited wholesaler or pharmacy networks and some product sales may be understated for lower volume products, which could include orphan drugs.

Source: IQVIA MIDAS MAT Dec 2016; *Estonia, Greece, Latvia & Luxembourg Retail Panels Only; Orphan drugs list from EMA Oct 2017 and Orphanet July 2016 downloads; Sales in Euros (absolute); Total Market includes Rx & non Rx
Despite the usually high unmet need in rare diseases, orphan drugs face challenges with pricing, reimbursement and access.

**Kalydeco**
- Experienced substantial access delays due to price – first sales 3 years after launch.

**Vertex**
- Refused £500m offer over 5 years from NICE for Cystic Fibrosis drug **Orkambi**. Current cost is £100k/year.

**Pfizer**
- Almost withdrew **Bosulif** from the market due to high AMNOG rebate.

**Recommendation**
- To not reimburse **Translarna** for treatment of Duchenne Muscular Dystrophy.

**US insurers**
- Are not convinced there is a demonstrated clinical benefit to **Exondys 51**, following only one trial of 12 patients and are pushing back on paying for the treatment.

**Challenging price-related market access**
Restricted or negative outcomes are becoming more common in Orphan Medicines assessments.


<table>
<thead>
<tr>
<th>Year</th>
<th>Positive outcome</th>
<th>Restrictive outcome</th>
<th>Negative outcome</th>
</tr>
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<tbody>
<tr>
<td>2013-2014</td>
<td>100%</td>
<td>11%</td>
<td>3%</td>
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<tr>
<td>2016-2017</td>
<td>86%</td>
<td>50%</td>
<td>9%</td>
</tr>
<tr>
<td>2013-2014</td>
<td>50%</td>
<td>21%</td>
<td>28%</td>
</tr>
<tr>
<td>2016-2017</td>
<td>51%</td>
<td>75%</td>
<td>8%</td>
</tr>
<tr>
<td>2013-2014</td>
<td>24%</td>
<td>68%</td>
<td>17%</td>
</tr>
<tr>
<td>2016-2017</td>
<td>100%</td>
<td>87%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Positive = full access as per label; Restricted = access but with label restrictions; Negative = no access granted.
The annual cost of the majority of orphan medicines in Europe is below $50,000, while the median annual cost per OD in the US is ~$32,000.

Orphan Drug Distribution by Annual Cost (average list price by indication), EU 2017

- 53% < USD 50,000
- 23% USD 50,001 – USD 200,000
- 13% USD 200,001 – USD 1,000,000
- 13% > USD 1,000,000


Price sources:
1. IQVIA Pricing Insights
2. IQVIA analysis
Payers developing collaborative measures to ‘get a grip’ on prices for rare disease medicines

Prioritisation of rare diseases will have to occur in order to manage budget impact

- EU commission exploring EU wide pharmaceutical price control measures, centred around collaboration and price transparency
- Joint purchasing agreement focused on Orphan drugs
  - Pioneered by Netherlands and Belgium
  - Joined by Luxembourg and Austria
  - Ireland announced it would join
- Dutch insurers introducing joint hospital purchasing schemes for biologics
- Italy restricting confidential pricing agreements
- Sweden increasing joint purchasing of high cost drugs across county councils
- Possible reduction of threshold for automatic additional benefit in Germany
- Bulgaria and Romania have entered an agreement to jointly negotiate pricing and availability
- Greece, Portugal, Spain and Italy have called for greater collaboration within the EU to drive down prices

Globally:
- Further establishment of registries
- Continued use of Outcomes-based agreements

NHS England commercial effectiveness team negotiating after NICE rejection. Introduction of real world studies combined with price negotiation
Average NICE and SMC ICER of orphan and non-orphan drugs (drug with positive recommendations only)

- For recommended technologies the ICERs of orphans are almost 2 times higher for orphans than for non-orphans
- These data suggest that both organizations may be implicitly adjusting their willingness to pay for medicines that target rare diseases, although in the case of NICE the decisions made on oncology drugs (orphan and non-orphan) will also be influenced by application of the End-of-Life (EoL) guidance. In

<table>
<thead>
<tr>
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<th>SMC</th>
<th>NICE</th>
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<tbody>
<tr>
<td>Orphan drugs</td>
<td>£46,211</td>
<td>£43,918</td>
</tr>
<tr>
<td>Non-orphan drugs</td>
<td>£24,090</td>
<td>£25,051</td>
</tr>
</tbody>
</table>

Sources: SMC [https://www.scottishmedicines.org.uk/](https://www.scottishmedicines.org.uk/); NICE [https://www.nice.org.uk/](https://www.nice.org.uk/)

The research proposes one general method for establishing a reasonable price for an orphan drug, based on the proposition that rates of return for investments in developing orphan drugs should not be greater than the industry average.

There is a growing tendency towards increased need for real world evidence, and orphan drugs are not insulated from this

**Poor real-world drug performances and major safety issues**
Recent failures of high profile products to demonstrate outcomes e.g. interferons for MS, ezetimibe for CVD, and major safety issues e.g. Actos and Avandia for diabetes, have led to increased clinical scrutiny from payers

**Increased at-launch data expectation**
More critical assessment of efficacy, safety, tolerability and adverse event data at launch

**Post-launch requirements for real world evidence**
Move to re-evaluate products post-launch, when limited trial data is available at launch

- Payers increasingly insisting on RWE studies to justify costs and more importantly balance risk
- It can be difficult to demonstrate the value in the rare disease area as it is often not possible to do longitudinal natural history studies due to limited patient registry availability
- Added benefit that can’t be quantified now, and will be defined later based on clinical experience
- Usually approved through conditional approval, still investing in clinical trials
- Predictive analytics should play an important role in identifying patients in the future

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Launching in rare diseases - Market challenges and launch requirements

- pending local legal approval-
Strensiq has come about as a new ‘managed access agreement’.

It will broaden access of asfotase alfa to infants, children and adult patients with paediatric-onset HPP, who experience the most disabling symptoms and are expected to benefit most from therapy.

It is a novel deal because it is a value-based risk sharing agreement to provide wider cost-effective access for patients, informed by their first-hand experience of the ongoing impact that treatment is having on their health and quality of life.

The MA Agreement allows for a five year period to gather real-world data about how well the treatment benefits patients, before longer term commissioning decisions are taken.
In the UK, IQVIA & GeL announced 5 year partnership to enable Real-World clinical-genomics research and trials in Life Sciences

• Genomic data
  ✓ Genomics expertise
  ✓ Genomics data and specimen pipeline
• Technology
  ✓ Genomics data management
  ✓ Privacy & data governance
• Network
  ✓ NHS knowledge and connections
  ✓ Discovery forum
  ✓ GeCIP
• Genomics development
  ✓ Data interpretation

Genomic data is a critical element to transform clinical research and healthcare delivery

• Clinical data management
  ✓ Clinical data models (eg, OMOP)
  ✓ International data curation & standardization
• Technology
  ✓ E360™
  ✓ Privacy Analytics
• Industry engagement
  ✓ Established customer base
• CRO, trials and network
• Healthcare analytics services to NHS

IQVIA and Genomics England Launch the First Real-World Research Platform with Integrated Clinical and Genomic Data

Matt Hancock the Secretary of State for Health and Social Care, announced an ambitious vision for genomic healthcare in the UK...

“Expansion of the 100,000 Genomes Project to one million whole genomes sequenced by NHSE and UK Biobank in the next five years”

“From 2019, the NHS will offer whole genome analysis for all seriously ill children with a suspected genetic disorder, including those with cancer. The NHS will also offer the same for all adults suffering from certain rare diseases or hard to treat cancers”

“An aspiration to sequence 5 million genomes in the UK within the next five-year years”
Patient identification in rare disease

**Case study: Nephronophthisis (NPHP)**

- **Nephronophthisis (NPHP)** is a group of autosomal recessive renal diseases
- **Rare** with variable prevalence (1 in 50,000 in Canada, 1 in 100,000 in Finland, 1 in 922,000 in US)
- Most common genetic cause of End Stage Renal Disease (ESRD) in children and young adults
- Multiple genes associated with NPHP (up to 22)
- NPHP Type 1 is most common disorder, caused by total homozygous deletion of NPHP1 gene

- Identified 12 patients with homozygous NPHP1 deletions
- All previously undiagnosed
- At least 9 had chronic kidney disease with presentations consistent with NPHP
- Follow up includes scanning for additional patients and analyzing HES data to better understand disease history

Source: Hildebrandt & Zhou - JASN June 2007, 18 (6) 1855-1871; DOI: https://doi.org/10.1681/ASN.2006121344
What is the role of Orphan drugs in an increasingly segmented world?

<table>
<thead>
<tr>
<th>Environment</th>
<th>Today</th>
<th>Next 5 years</th>
<th>Next 10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Value growth is highly concentrated into <strong>specialty TAs</strong> and developed country markets</td>
<td>• Genetic profiling and <strong>biomarkers</strong> create new payer propositions</td>
<td>• Markets radically re-defined by <strong>genotype, biomarker</strong> and other patient specific characteristics</td>
<td></td>
</tr>
<tr>
<td>• Stakeholder complexity grows</td>
<td>• Diseases are being divided and subdivided into smaller categories, treating <strong>smaller sub-groups of patients</strong>, with high per capita prices</td>
<td>• <strong>New payment models</strong> for highly expensive products: payment by use, payment by outcome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• <strong>Patients increasingly activist</strong></td>
<td>• <strong>Regulatory process adapted</strong> to accommodate advances in science and technology</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Company</th>
<th>Today</th>
<th>Next 5 years</th>
<th>Next 10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>• New roles to adapt to <strong>growing stakeholder complexity</strong></td>
<td>• <strong>Post-marketing commitments</strong> and RWI more frequently required</td>
<td>• Companies will be addressing unique value propositions by patient- the “<strong>patient as CEO</strong>”</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Accurate patient identification and <strong>diagnosis tools</strong> developed</td>
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