Characterizing the value of orphan drugs in an HTA environment

Indranil Bagchi, Ph.D.
Vice President, Market Access
Specialty Care, Pfizer

CADTH SYMPOSIUM
May 6, 2013
Agenda

• Background
• Regulatory Approval vs. Health Technology Assessment (HTA)
• Evolving payer policy shifts
• Case for Action
• Summary
Rare diseases represent great opportunity and great variability

Rare diseases are perceived to have attractive dynamics...

- Accelerated time-to-market
- Areas of high unmet need
- Limited competition
- Pricing commensurate with innovation
- Focused commercial resources
- Support of advocacy groups in obtaining access

...but not all rare disease are created equal

- Unclear regulatory pathways
- Challenges in establishing clinical endpoints
- Use of off-label or generic drugs
- Difficult-to-measure population size, often with variability in severity and need
- Often long time to diagnosis, lack of natural history, unclear pathways
- Greater complexity of therapy delivery
- Greater need for support systems (e.g., reimbursement, education, logistics)

..and they’re becoming increasingly competitive.

- More markets with multiple approved agents, e.g.:
  - Gaucher’s,
  - CF-associated respiratory infections,
  - Hereditary angioedema
- More companies with focused rare disease strategies and intense BD/L efforts

Pfizer Rare Disease
Accelerated approvals increasingly common for Orphan Drugs….

- Requirement to conduct studies that completely satisfy the needs of a classic design would prevent many orphan medicines from receiving market authorization.
- The conduct, analysis and interpretation of studies in rare disorders are constrained by the prevalence of the disease.
- Need to find a balance between accelerating patients’ access to treatments, and the need to make the best possible assessment of the risks and benefits of new medicines.

*Other includes: Nithiodote (approval based on literature case reports only) and Makena (approved with Phase IV data in label)

Sources:
4. ClinicalTrials.gov, FDA Databases
..... however, market access has often lagged behind

- Under standard methods of HTA, orphan drugs do not usually prove to be cost-effective

- There is more to decision making than strict application of cost-effectiveness thresholds

- Multi-attribute decision-criteria:
  - Societal value
  - Seriousness of the health condition
  - Availability of treatment options
  - Cost to the patient if the drug is not reimbursed
  - Technical vs. Allocative efficiency
### International HTA review: Fair, Flawed or Failing?

<table>
<thead>
<tr>
<th>Drug/Indication</th>
<th>Canada CDR</th>
<th>England NICE</th>
<th>Australia PBAC</th>
<th>Sweden TLV</th>
<th>France HAS</th>
<th>Scotland SMC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambrisentan Pulmonary arterial hypertension</td>
<td>LWC</td>
<td>--</td>
<td>LWC</td>
<td>LWC</td>
<td>DNL</td>
<td>LWC</td>
</tr>
<tr>
<td>Arsenic trioxide Acute promyelocytic leukemia</td>
<td>--</td>
<td>--</td>
<td>LWC</td>
<td>--</td>
<td>LWC</td>
<td>--</td>
</tr>
<tr>
<td>Azacitidine Acute myeloid leukemia</td>
<td>--</td>
<td>--</td>
<td>LWC</td>
<td>--</td>
<td>LWC</td>
<td>DNL</td>
</tr>
<tr>
<td>Dasatinib Chronic myeloid leukemia</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>L</td>
<td>LWC</td>
<td>LWC</td>
</tr>
<tr>
<td>Eculizumab Paroxysmal nocturnal haemoglobinuria</td>
<td>DNL</td>
<td>--</td>
<td>DNL</td>
<td>--</td>
<td>LWC</td>
<td>DNL</td>
</tr>
<tr>
<td>Idursulfase Hunter Syndrome (MPS II)</td>
<td>DNL</td>
<td>--</td>
<td>DNL</td>
<td>--</td>
<td>LWC</td>
<td>DNL</td>
</tr>
<tr>
<td>Imatinib mesylate Chronic myeloid leukaemia</td>
<td>--</td>
<td>LWC</td>
<td>--</td>
<td>--</td>
<td>LWC</td>
<td>LWC</td>
</tr>
<tr>
<td>Lenalidomide Multiple myeloma</td>
<td>--</td>
<td>LWC</td>
<td>LWC</td>
<td>LWC</td>
<td>LWC</td>
<td>DNL</td>
</tr>
<tr>
<td>Sorafenib tosylate Hepatocellular carcinoma</td>
<td>DNL</td>
<td>DNL</td>
<td>LWC</td>
<td>case by case</td>
<td>LWC</td>
<td>DNL</td>
</tr>
</tbody>
</table>

**Key:** L = List; LWC = List with criteria; DNL = Do not list

**Source:** Adapted from Euro Observer. Winter 2010 v12(4); CDR website accessed April 22, 2013

[www.cadth.ca/en/products/cdr/search](http://www.cadth.ca/en/products/cdr/search)
Examples of pan-European HTA and access initiatives

Attempting to address disparities in access to orphan medicines across Europe:
- Evidence gap between regulatory approval and reimbursement
- Inconsistent approaches to evaluating relative benefit of medicines
- Perception that high prices are unjustifiable and unaffordable in many countries

Clinical Added Value of Orphan Medicinal Products (CAVOMP)
- Dialogue with payers and regulators on development plans to support early access
- Concepts developed by EURORDIS, industry and national experts in rare diseases

EUnetHTA joint action on HTA
- Network of HTA agencies developing coordinated advice processes, agreed methodologies and pilots of centralised relative effectiveness assessment, including orphan drugs

Mechanism of Coordinated Access to Orphan Medicinal Products (MOCA)
- Transparent Value Framework to set out multiple criteria to apply in value assessment of orphan drugs
- EU Commission, member state payer groups, industry and EURORDIS participated
Evolving national payer policy shifts

- German AMNOG healthcare legislation requires an early benefit assessment for all new therapies, with products required to show additional benefit vs. standard of care
- Orphan medicines receiving EMA approval are assumed to have an additional benefit
- Initial misalignment between HTA agency IQWiG and Joint Federal Committee (G-BA) now addressed, with elimination of IQWiG assessment below €50mn/year threshold

- NICE issued supplementary advice for appraising treatments which may be life extending, when such treatments have an ICER above usual threshold
- Advisory Group for National Specialised Services (AGNSS-England) “Social Value Framework” - multi-criteria decision analysis where cost effectiveness represents only one of many criteria
- Under future consideration, now that AGNSS is folded under NICE

- Belgium and Netherlands: Cost effectiveness not required for orphan drugs
- Spain: Orphan drugs subject to a lower discount (4%) vs. non-orphan drugs (7.5%)
- France: Paid early access programs (ATU) for medicines that fulfill certain criteria
The case for action

What’s required for Evidence Optimization:

• Alignment between Regulators and Payers on evidence requirements for orphan drugs, that take into account the specific issues facing rare diseases
  – Small number of patients in clinical trials
  – Need inclusive attitudes to evidence and flexible approaches to assessment, that take into account the rarity of the condition
  – Degree of fundamental understanding of the natural history of disease
  – Limitations in identification and diagnosis of patients
  – Urgency of patient need

• Early dialogue with Regulators and Payers, so that products developed are useful, useable and used
  – Even following expedited or conditional approval, reimbursement negotiations can delay access for patients in need
  – Create funded early access program for orphan drugs
Ensuring a sustainable model

Patients suffering from rare diseases should be entitled to the same quality of care and access to beneficial treatments, as patients suffering from more common diseases

- Patent protection and R&D incentives
  - Inefficient for society at large to limit access and discourage future investment
- Registries to address “uncertainties”
- Orphan drugs should be excluded from national austerity measures meant to reduce healthcare spending
- Risk sharing and coverage with evidence development (on a case by case basis)
Summary

• Though regulatory approval is often on an accelerated basis for orphan drugs, **market access** has often lagged behind

• There needs to be **alignment** between Regulators and Payers on evidence requirements for orphan drugs, taking into account the specific issues facing rare diseases

• There needs to be a **balance** between accelerating patients’ access to treatments, and the need to make the best possible assessment of the risks and benefits of new medicines

• A **sustainable** business model is needed, to ensure patients suffering from rare diseases are entitled to the same quality of care and access to treatments as those suffering from more common diseases
Impact on patient health is the ultimate bottom line

Our Mission:
Eradication, Remission and Relief of Serious Diseases

We sustain this commitment through:

• A portfolio of meaningful medicines and vaccines
• Adding value through ongoing clinical exploration
• Engaging customers and stakeholders to ensure optimal patient outcomes and positive customer experience
Your Questions
BACKUP
Common Drug Review (CDR) recommendations regarding the reimbursement of rare disease medications

<p>| Number of recommendations on rare disease drugs | 20 |
| Number of positive recommendations (List) | 6 |
| Number of negative recommendations (Do not list) | 14 (70%) |
| Number of recommendations with <strong>therapeutic concerns</strong> as main criteria for not listing | 8 (57%) |
| Number of recommendations with <strong>economic concerns</strong> as main criteria for not listing | 6 (43%) |
| Number of negative recommendations with <strong>economic concerns</strong> ($ or ICER) cited as negative factor | 14 (100%) |</p>
<table>
<thead>
<tr>
<th>Product (brand)</th>
<th>Indication</th>
<th>Recommendation</th>
<th>Reason for DNL</th>
<th>CDEC Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Replagal</td>
<td>Fabry Disease</td>
<td>DNL</td>
<td>T</td>
<td>Impact on clinically meaningful outcomes has not been proven. High average acquisition $239,000$. No CEA supporting the value of this product.</td>
</tr>
<tr>
<td>Zavesca</td>
<td>Gaucher disease</td>
<td>DNL</td>
<td>T</td>
<td>Insufficient clinical evidences on its impact on key hematologic and bone complications. Clinical benefit over supportive therapy must be supported to validate the costs ($118,000 annually).</td>
</tr>
<tr>
<td>Fabrazyme</td>
<td>Fabry Disease</td>
<td>DNL</td>
<td>T</td>
<td>Impact on clinically meaningful outcomes not proved. Unlikely to be cost-effective at sub. price ($290,599/y) (No CEA supporting the value).</td>
</tr>
<tr>
<td>Aldurazyme</td>
<td>Mucopolysaccharidosis 1 (MPS 1), Hurler, Scheie</td>
<td>DNL</td>
<td>T</td>
<td>No evidence for improvement in clinical endpoints and it can result in life threatening adverse events. At sub. Price, ($434,000/y), not cost-effective according to traditional criteria.</td>
</tr>
<tr>
<td>Somavert</td>
<td>acromegaly</td>
<td>DNL</td>
<td>E</td>
<td>Significant clinical benefit on IGF-1 level, but no QOL benefit. ICER ($136,000/QALY) is high and likely to be underestimated (Uncertain assumptions not supported by clinical data).</td>
</tr>
<tr>
<td>Nexavar</td>
<td>Cancer, Renal cell carcinoma</td>
<td>DNL</td>
<td>E</td>
<td>CEA was not carried-out using proper survival data. The survival effectiveness and true C-E of this medication are uncertain.</td>
</tr>
<tr>
<td>Sutent</td>
<td>Gastrointestinal stromal tumour</td>
<td>LWC</td>
<td>N/A</td>
<td>Significant improvement in progression free survival, Costs similar to those of the comparator.</td>
</tr>
<tr>
<td>Exjade</td>
<td>Iron overload</td>
<td>LWC</td>
<td>N/A</td>
<td>Comparative effectiveness and safety over deferoxamine remain unclear. More $ than comparator and the ICER might be inaccurate (based on assumptions not supported by clinical data).</td>
</tr>
<tr>
<td>Sutent</td>
<td>Metastatic renal cell carcinoma</td>
<td>DNL</td>
<td>T</td>
<td>No evidence supporting the use of sunitinib in patients who have failed cytokine-based therapy. The ICER is likely to be wrong.</td>
</tr>
<tr>
<td>Myozyme</td>
<td>Pompe’s disease</td>
<td>LWC</td>
<td>N/A</td>
<td>Improve survival in patient with infantile-offset pompe’s disease. Probably not cost-effective using traditional criteria.</td>
</tr>
</tbody>
</table>

DNL: Do not list; LWC: List with criteria; T: Therapeutic concerns; E: Economic concerns; N/A: Non applicable
<table>
<thead>
<tr>
<th>Product (brand)</th>
<th>Indication</th>
<th>Recommendation</th>
<th>Reason for DNL</th>
<th>CDEC Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elaprase</td>
<td>MPS II, Hunter Syndrome</td>
<td>DNL</td>
<td>T</td>
<td>The clinical significance of its effect is not established. No effect on QoL, hosp. Rate, Pain. Average annual cost of $657,000 not justified</td>
</tr>
<tr>
<td>Xyrem</td>
<td>Narcolepsy</td>
<td>DNL</td>
<td>E</td>
<td>Based on the CEA results and considering uncertainties in clinical evidence, the cost-effectiveness has not been demonstrated.</td>
</tr>
<tr>
<td>Soliris</td>
<td>Paroxysmal nocturnal hemoglobinuria</td>
<td>DNL</td>
<td>E</td>
<td>Eculizumab would not be considered cost-effective without a substantial reduction in the submitted price.</td>
</tr>
<tr>
<td>Ilaris</td>
<td>Cryopyrin-associated Periodic Sx (CAPS)</td>
<td>DNL</td>
<td>T</td>
<td>Clinical studies were too short to assess harm-benefit ratio for drug. No QoL data. Limitations in CEA (method no specified).</td>
</tr>
<tr>
<td>Kuvan</td>
<td>Phenylketonuria</td>
<td>DNL</td>
<td>E</td>
<td>Insufficient patient details to identify subpopulation for which Kuvan would provide clinical benefit that is also cost effective. Annual costs: $24-$180K. Price of comparators (if there are any) were not reported.</td>
</tr>
<tr>
<td>VPRIV</td>
<td>Gaucher Disease</td>
<td>LWC</td>
<td>N/A</td>
<td>Non inferior and cheaper than comparator. VPRIV could address drug shortage seen with cerezyme. No impact on bone data and QoL</td>
</tr>
<tr>
<td>Cayston</td>
<td>Cystic Fibrosis with Pulmonary Pseudomonas Aeruginosa infections</td>
<td>LWC</td>
<td>N/A</td>
<td>Limited clinical trial data and additional costs associated with comparator. Patient input stressed the need for additional antibiotic treatment options</td>
</tr>
<tr>
<td>Revolade</td>
<td>Chronic Immune Thrombocytopenic Purpura</td>
<td>DNL</td>
<td>T</td>
<td>CEA analysis included effectiveness data not based on RCT. Clinical data possibly overestimated and standard of care should have been used as comparators. Not Cost-effective according to standard criteria</td>
</tr>
<tr>
<td>Banzel</td>
<td>Lennox-Gastaut; Adjunctive Tx of Seizures</td>
<td>LWC</td>
<td>N/A</td>
<td>Less $ alternatives must be ineffective or not appropriate. Caregivers QoL affected - Need drug publically funded due to high unemployment and reduced access to private insurance</td>
</tr>
<tr>
<td>Kalydeco</td>
<td>Cystic Fibrosis with G551D Mutation</td>
<td>DNL</td>
<td>E</td>
<td>Improvements in patient-reported respiratory symptoms. ICERs range from $2 to $9 million per QALY; not cost-effective at the sub. price ($306,600/y). Unmet need in the treatment of CF could potentially be met by ivacaftor.</td>
</tr>
</tbody>
</table>

DNL: Do not list; LWC: List with criteria; T: Therapeutic concerns; E: Economic concerns; N/A: Non applicable