Introduction

- Researchers are often tasked with developing global cost-effectiveness models to support the launch of a new product in multiple settings.

- Cost-effectiveness models are used to gain reimbursement in many countries and are required by many decision-making bodies (e.g., NICE in the UK, PBAC in Australia).

- Development of a global cost-effectiveness model requires consideration of HTA requirements in the settings of interest.
  - While these differ across jurisdictions (e.g., UK, Canada, Australia), in general the requirements can be handled in one global model.

- Orphan drugs pose unique challenges in preparing for discussions with decision makers across settings, as HTA and reimbursement requirements for orphans vary significantly.
Introduction (2)

- New products for rare diseases are expensive due to the small number of patients eligible for treatment

- Orphan drugs are priced so high that even drugs with a favorable clinical profile are not considered cost-effective relative to the status quo

- This poses a challenge for decision makers, as other factors come into play when considering reimbursement of orphan drugs (ethical, political, social)

- Researchers and manufacturers should be aware that preparing for the global launch of an orphan drug is very different from preparing for launch of a non-orphan

Focus for Today

- Note that there are several steps involved in introducing an orphan drug to market
  - Market authorization (clinical evidence)
  - Availability (indications for which drug is approved)
  - Access (HTA guidance, reimbursement decisions, cost to patients)

- Each of these comes with its own challenges due to the small number of patients eligible to receive the drug

- Focus today is on access—specifically
  - How orphans are handled by HTA agencies globally?
  - What criteria are used to make decisions?
To Start…
Variability by Country: Definition of “Rare”

• In Australia, a condition is considered rare if it affects 2,000 individuals in the entire population (approximately 1 in 10,000)

• In the EU a condition is deemed ‘rare’ if its frequency is 1 in 2,000
  – “Ultra-orphan” in the UK: <1,000 cases in England & Wales

• In the US, a rare disease is one that affects fewer than 200,000 persons (~1 per 1,500) (NIH)

• In Canada, only the provinces of Ontario and Alberta have established definitions of ‘rare’ diseases
  – Ontario’s current definition of ‘rare’ ranges between 1 per 100,000 to 1 per 150,000
  – Alberta defines a ‘rare’ disease as a genetic disorder that occurs in less than 1 in 50,000 Canadians or fewer than 50 Albertans

HTA Assessment of Orphan Drugs Around the Globe

• While country-specific requirements exist, orphans are treated differently across the world
  – In Australia, orphan drugs are assessed separately from non-orphans, using very strict criteria
  – In Canada, Ireland, & Scotland, orphans go through same process as all other drugs
  – In the UK, NICE no longer has responsibility for orphans; instead they are assessed by a separate group
  – In Belgium and other countries, a full pharmacoeconomic evaluation is not required for orphans
  – In Germany, the requirement to demonstrate additional benefit is assumed to be shown by EMA approval and orphan drug status, and is therefore waived unless annual gross sales exceed 50 million Euros

• In most cases, criteria other than cost-effectiveness are used to inform reimbursement of orphans, including:
  – Severity of the disease
  – Availability of other therapies to treat the disease
  – Cost to the patient if therapy if not reimbursed
Reimbursement of Orphan Drugs Around the Globe

<table>
<thead>
<tr>
<th>Decision Process for Reimbursement?</th>
<th>Australia</th>
<th>Canada</th>
<th>Germany</th>
<th>U.K.</th>
<th>U.S.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Different from other drugs</td>
<td>Same as for other drugs nationally*</td>
<td>“Different” from other drugs</td>
<td>Different from other drugs</td>
<td>Varies by plan</td>
</tr>
</tbody>
</table>

| Specific Orphan drug committee?     | Yes-Life Saving Drugs Program (LSDP) | No* | No | Yes-Advisory Group for National Specialized Services (AGNSS) | Varies by plan |

| Separate budget for orphans?        | Yes-separate appropriation item in the budget | No* | No | Yes-separate item in the budget | No |

* The provinces of Alberta and Ontario each have guidance in place for the coverage of health care services for treatment of orphan diseases.

Some Examples: Australia

- In Australia, Pharmaceutical Benefits Advisory Committee (PBAC) makes national funding decisions for public healthcare system
- Since 1995, the Life Saving Drug Program (LSDP) has provided subsidized access for life saving drugs meeting specific criteria
- Reimbursement for life saving drugs is provided through a separate budget
- First hurdle is to meet two conditions in PBAC submission:
  1. PBAC accepts evidence that life expectancy would be significantly extended as a direct consequence of the drug
  2. Drug accepted as clinically effective, but rejected by PBAC on cost-effectiveness grounds
Some Examples: Australia (2)

• Following this, the drug must meet each of the following criteria:
  1) There is a rare but clinically definable disease for which the drug is regarded as a proven therapeutic modality (ie, approved for that indication by the TGA)
  2) The disease is identifiable with reasonable diagnostic precision
  3) Epidemiological and other studies provide evidence acceptable to the PBAC that the disease causes a significant reduction in age-specific life expectancy for those suffering from the disease
  4) There is evidence acceptable to the PBAC to predict that a patient's lifespan will be substantially extended as a direct consequence of the use of the drug
  5) The drug must be accepted as clinically effective, but rejected for Pharmaceutical Benefits Scheme listing because it fails to meet the required cost-effectiveness criteria

Some Examples: Australia (3)

6) There is no alternative drug listed on the PBS or available for public hospital in-patients which can be used as lifesaving treatment for the disease. However, the availability of an alternative drug under the LSDP does not disqualify the proposed drug from consideration for the LSDP

7) There is no alternative therapeutic modality (eg, surgery, radiotherapy) which is recognised by medical authorities as a suitable and cost effective treatment for this condition

8) The cost of the drug, defined as the cost per dose multiplied by the expected number of doses in a one year period for the patient, would constitute an unreasonable financial burden on the patient or his/her guardian
Some Examples: Australia (4)

Further……

B) Consideration and advice will also be provided by the PBAC, if applicable, on:

1) The proposed price of the drug compared with the effective price of the drug in comparable overseas markets
2) The proposed cost of the drug compared with the cost of comparable drugs, if any, that are already funded through the LSDP

Some Examples: Australia (5)

To date, funds have been made available for the following therapies:

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imiglucerase (Cerezyme®)</td>
<td>Gaucher disease</td>
</tr>
<tr>
<td>Miglustat (Zavesca®)</td>
<td>Fabry disease</td>
</tr>
<tr>
<td>Agalsidase alfa (Replagal®)</td>
<td>Mucopolysaccharidosis Type I (MPS I)</td>
</tr>
<tr>
<td>Agalsidase beta (Fabrazyme®)</td>
<td>Mucopolysaccharidosis Type II (MPS II)</td>
</tr>
<tr>
<td>Laronidase (Aldurazyme®)</td>
<td>Mucopolysaccharidosis Type VI (MPS VI)</td>
</tr>
<tr>
<td>Idursulfase (Elaprase®)</td>
<td>Infantile-onset Pompe disease</td>
</tr>
<tr>
<td>Galsulfase (Naglazyme®)</td>
<td>Paroxysmal Nocturnal Haemoglobinuria (PNH)</td>
</tr>
<tr>
<td>Alglucosidase alfa (Myozyme®)</td>
<td></td>
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<tr>
<td>Eculizumab (Soliris®)</td>
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Some Examples: Canada

• In Canada, Canadian Expert Drug Advisory Committee (CEDAC) makes recommendations to Drug Plans for funding
• The provinces of Ontario & Alberta have their own guidelines around coverage for orphans
• Drugs for rare diseases (DRD) framework developed in Ontario in 2008
  – Disease defined as “rare” if affects 1 in 100,000 to 1 in 150,000
• Key steps in the evaluation of DRDs include:
  1) Determine the ‘rarity’ of disease based on Ontario’s current working definition
  2) Review natural history of the disease
  3) Assess the potential effectiveness of treatment using best available evidence
  4) Evaluate total budget impact
  5) Identify additional follow-up data required
  6) Consider ‘social values’ based on input of Ontario’s Citizen Council

Some Examples: Canada (2)

• Review of a drug under DRD framework is more extensive than non-orphan review by Ontario Committee to Evaluate Drugs (CED)
• Decisions are made by the committee with the help of disease simulation and pharmacoeconomic models
• Submission requirements:
  – Manufacturers must follow Ontario CED’s standard submission guidelines including the submission of a budget impact analysis
  – Manufacturer responsible for compiling rationale for review of the new drug through the DRD framework (ie, establish ‘rarity’ of disease, provide prevalence and incidence of disease, results based on a randomized-controlled trial, data on current treatment options, clinically meaningful parameters, specific diagnostic tools etc)
### Some Examples: Canada (3)

To date, DRD has funded the following therapies:

<table>
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<tbody>
<tr>
<td>Miglustat (Zavesca®)</td>
<td>Niemann Pick Type C (NPC)</td>
</tr>
<tr>
<td>Alglucosidase alfa (Myozyme®)</td>
<td>Infant and adult Pompe disease</td>
</tr>
<tr>
<td>Idursulfase (Elaprase®)</td>
<td>Mucopolysaccharidosis Type II (MPS II)</td>
</tr>
<tr>
<td>Laronidase (Aldurazyme®)</td>
<td>Mucopolysaccharidosis Type I (MPS I)</td>
</tr>
<tr>
<td>Canakinumab (Ilaris®)</td>
<td>Cryopyrin-Associated Periodic Syndrome (CAPS)</td>
</tr>
</tbody>
</table>

- DRD framework has been utilized to assess the following drugs which were *not* granted funding:
  - Galectose (Naglazyme®) for MPS VI
  - Zolinza (Vorinostat®) for cutaneous T-Cell lymphoma (CTCL)

http://www.health.gov.on.ca/english/providers/program/drugs/ced_rec_table.html

### In sum...

- HTA process for reimbursement of orphan drugs varies across settings
- Within the framework of decision making about orphans, role of cost-effectiveness varies by setting
- Other priorities that play a key role in reimbursement decisions include:
  - Clinical benefit (high bar)
  - Ethical/moral considerations (equitable access, cost to patient)
  - Severity of disease, availability of alternatives……etc.
- Although all countries are wrestling with the same challenges with respect to reimbursement of orphans, they approach it in slightly different ways
- This has resulted in differential *access*, depending on what country you are in
- It is in the best interests of patients, payers, HTA bodies, policy makers, and manufacturers if the approach was consistent across jurisdictions, and further—if the approach was multi-faceted