Expensive Drugs for Rare Diseases

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I. What is an orphan drug?
II. What decisions have been made?
III. Do they deserve special status?
IV. What opportunities remain?
I. What is an orphan drug?
II. What decisions have been made?
III. Do they deserve special status?
IV. What opportunities remain?

My perspective:
Hospital HTA Producer + User,
MOH Provincial Formulary Committee
An old adage . . .

When you hear hoofbeats . . .
‘Orphan’ Drugs in Canada

What is an ‘orphan’?

- Drug for a rare disease that is debilitating or life-threatening (<1/1000)
- 6000 rare diseases have been defined (most are of genetic origin)
- ~3 million Canadians will suffer from a rare disease, condition, or syndrome in their lifetime

Unknown = Unloved?

Few Customers = No Industry Incentive
‘Orphan’ Drugs in Canada

Examples of ‘orphan’ drugs

- Cerezyme
- Myozyme
- Aldurazyme
- Fabrazyme
- Gleevec

Many more in the pipeline...
Incentives to drug companies include:

- Market exclusivity
- Reduction of licensing fees
- Assistance with marketing applications
- Direct access to centralized procedure for marketing authorization
- Provision of specific research grants (US)

In Canada, no specific ‘Orphan Drug’ policy exists
Is the current approach to reviewing new drugs condemning the victims of rare diseases to death? A call for a national orphan drug review policy

It is virtually impossible to assess cost-effectiveness of treatments for rare diseases using conventional criteria.

Should Canadian patients be denied access to potentially effective new treatments for formerly untreatable and serious diseases only because it is virtually impossible to evaluate the cost-effectiveness of those treatments using conventional criteria?
Cost informs the decision

Cost is one consideration,
But never the only consideration
Expensive Drugs
Rare Diseases

True Heart-Rending Stories

Two Examples:
1. Dominic*  
2. Darla*

*Details have been modified to respect confidentiality
Expensive Drugs for Rare Diseases

I. Patient Perspective
II. Hospital Perspective
III. Ministry of Health Perspective
Expensive Drugs for Rare Diseases

I. Patient Perspective
II. Hospital Perspective
III. Ministry of Health Perspective
Dominic: Fabry’s Disease

Fabry’s Disease
- Pain
- Renal Dysfunction
- Cardiovascular Disease
- Premature Death

Treatment = Supportive
Hurler’s Syndrome

- Respiratory Dysfunction
- Musculoskeletal Deformity
- Cardiovascular Disease
- Neurologic Decline
- Premature Death

Treatment = Supportive +/- BMT

Darla: Hurler’s Syndrome (MPS I)
Expensive Drugs for Rare Diseases

I. Patient Perspective
II. Hospital Perspective
III. Ministry of Health Perspective
**Hospital Action:**
Rapid HTPA

**What are the Benefits (Triple E)?**

**What are the Risks (Triple E)?**

**Risks worth the Benefits (B:R)?**

**What are the Tradeoffs (HTPA)?**

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**Aldurazyme® (Laronidase):**
Enzyme Replacement Therapy for Hurler’s Syndrome

**A. Background**

*Mucopolysaccharidosis I (MPS I)* is a *lysosomal* storage disorder with a chronic, progressive, debilitating, and life-threatening course. (Wraith 2004) The disease is *autosomal recessive,* pantocic, and occurs with an incidence of ~ 1/100,000 live births.

In MPS I, deficient activity of the enzyme alpha-L-iduronidase leads to accumulation of *glycosaminoglycans* (GAG), which ultimately results in compromised organ and tissue function.

MPS I is phenotypically heterogeneous, with diverse manifestations of symptoms that progress at variable rates. Patients with MPS I are classified into 3 clinical syndromes (Table I) which overlap in symptomatology and cannot be distinguished by routine enzyme or urinary GAG assays (Wraith 2004).

**Table I: MPS I Clinical Syndromes**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Symptomatology</th>
<th>Life Expectancy</th>
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<tbody>
<tr>
<td>Hurler</td>
<td>Severe</td>
<td>&lt; 10 years</td>
</tr>
<tr>
<td>Hurler-Scheie</td>
<td>Moderate</td>
<td>&lt; 25 years</td>
</tr>
<tr>
<td>Scheie</td>
<td>Mild</td>
<td>Sometimes normal</td>
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A major cause of morbidity and mortality in MPS I is respiratory insufficiency, with reduced lung
**Evidence**

- Clinically-Important Benefits: None found
- Surrogate Outcomes: FEV, 6-minute walk test

**Economics:** (None)

- Downstream hospitalization cost-savings (?)

**Ethics**

- Equity: Rule of Rescue
- Politically ‘positive’; Media assuaging
**Evidence:**

- Clinically-Important Risks: Infusion reaction
- Surrogate Outcomes: Infusion-related reactions (NNH = 6), usually mild

**Economics:**

- $120,000 – $900,000/yr (+ personnel)

**Ethics:**

- Inequitable: Why should ‘rare’ be ‘special’?
- Is ‘no’ discriminatory?
Social:

- Foregone health benefits elsewhere
- Premature acceptance of evidence; stifled research

Political:

- Would ‘no’ blackmark our pediatric genetics program?
- Legal precedent, politically sensitive
Hurler’s Syndrome

- Respiratory Dysfunction
- Musculoskeletal Deformity
- Cardiovascular Disease
- Neurologic Decline
- Premature Death

Treatment = Supportive +/- BMT
Dominic: Fabry’s Disease

**Fabry’s Disease**
- Pain
- Renal Dysfunction
- Cardiovascular Disease
- Premature Death

**Treatment** = Supportive
What did we decide?

Aldurazyme:
- Yes

Fabrazyme:
- No
Expensive Drugs for Rare Diseases

I. Patient Perspective
II. Hospital Perspective
III. Ministry of Health Perspective
**Recommendation:**
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that laronidase not be listed.

**Reasons for the recommendation:**
1. One six-month, double-blind, placebo controlled randomized controlled trial (RCT) in 45 patients reported a 5.6% mean improvement in forced vital capacity (95% CI 1.15-10.05), and a non-statistically significant median change in the six-minute walk test distance of 38.5 m (95% CI -2.0 to 79.0) in the laronidase group. The study also noted a mean reduction in liver size of 20.2% (p=0.001). The clinical significance of these physiological and anatomical measurements is unknown. No differences were noted in quality of life, as measured by the Childhood Health Assessment Questionnaire (in children) or the Health Assessment Questionnaire (in adults).
Recommendation:
CEDAC recommends that agalsidase beta not be listed.

Reasons for recommendation:
1. One 20-week randomized controlled trial (RCT) involving 58 people compared agalsidase beta with placebo and showed reduced interstitial capillary endothelial cell GL-3 levels. However, this trial failed to show a clinical benefit of agalsidase beta on a range of tests of neurologic, renal and cardiac function. The RCT reported no significant improvement in quality of life.

A second unpublished RCT involving 82 patients with a mean follow-up of 18 months compared agalsidase beta with placebo. The primary endpoint was the time to the first occurrence of a “clinically significant” renal, cardiac or cerebrovascular event and/or death. The manufacturer has requested that these results remain confidential, pending publication and pursuant to the Confidentiality Guidelines of the Procedures for CDR.

Two unpublished open-label extension trials of the first RCT mentioned above were also reviewed. In these observational trials, all patients received agalsidase beta for 30 and 42 months, respectively. The manufacturer has requested that these results remain confidential pursuant to the Confidentiality Guidelines of the Procedures for CDR.

Having reviewed all of the information mentioned above, it is CEDAC’s opinion that although this medication affects certain surrogate markers, its impact on clinically meaningful outcomes has not been proven in randomized trials or observational studies.
Is that fair?

Aldurazyme & Fabrazyme:

- CEDAC says ‘no’.
- Individual jurisdictions say ‘no’
- But, some hospitals say ‘yes’
- Internationally, funders say ‘yes’

Is institutional charity allowable, given the Canada Health Act?
Is that fair?

Who is Right?
### ‘Rarity’ = Special Status?

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Carte Blanche

Stifled Innovation
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Stifled Innovation

‘Credits’
“Reimbursement of laronidase would raise questions about equity, since drugs that have not been shown to be cost-effective for other diseases are not generally reimbursed”

CEDAC, Aldurazyme Final Recommendation, 2005
Given resources that do not meet all needs, money spent on one service means another service cannot be provided.

Funding decisions should not be posed as isolated questions.

Cost effectiveness thresholds are a shorthand way of accounting for opportunity cost; if decisions breach these norms they should be justified by principled argument.

The current system, which obscures the opportunity cost, is inefficient, unfair, and unsustainable given the growth in orphan drugs.

Burls et al. BMJ 2005;331:1019-21
Difficult decisions do have to be made within the NHS. Too often these decisions are made in secret. But they should know that we do support them and we know they have to keep within a budget. The NHS shouldn't be frightened of the public finding out about all this—they should discuss it more with the public. They'll only keep our confidence if they level with us about the difficult choices that have to be made.

Lay member, NICE Citizen’s Council
We need to learn how to make trade-offs between equity and efficiency that are explicit, principled, and generalisable and how to admit openly when there are treatments and services that are not being funded.

Burls et al. BMJ 2005;331:1019-21
Impact on Decision-making

High Impact Technology Evaluation Clinic

Impact on Decision-making

Budget Impact

Benefit Index

'No-Go'

'Go'

Numbers 1 to 35 represent different projects or technologies, with different colors and sizes indicating varying impacts.
If we fund Aldurazyme…

- Unknown clinical benefit
- Political ‘Correctness’
- Media Friendliness

What you 4Go …
- PCI = 2 lives
- APC = 0.75 lives
- L-Ampho = 4 lives
If we do not fund Aldurazyme…

What you Get …

- PCI = 2 lives
- APC = 0.75 lives
- L-Ampho = 4 lives

What you 4Go …

- Unknown clinical benefit
- Political ‘Correctness’
- Media-Friendliness
Provincial Disparity

Provincial Listings of Innovative Medicines Launched
(For Products Launched from September 1, 1999 to August 31, 2001)

Note: These statistics are based on the introduction of 143 products.
Drug Costs are the Second Largest Sector of Expenditure in Health Care Costs

(Canada: $130 Billion, 2004)

- Capital, $5.9
- Public Health, $8.7
- Other Institutions, $12.5
- Other, $11.2
- Physicians, $16.8
- Drugs, $21.8

Hospitals, $38.9, 30%

Other Health Care Prof., 16.7%
Develop a National Framework

- NPS has named orphan drugs as a priority
- Achieve universality and consistency (HCA)
- NPS recommendations + national funding

Without a National Framework

- Inequities in access will prevail
- Pressure on hospitals will continue
- (Reverse) rationing at the bedside will occur
At the very least . . .

Criteria for public funding should be defined along with the citizens of Canada

- When is deviation from conventional criteria allowed?

Best possible evidence should be required

- Require registries at the outset
- Define stopping rules
- New methodologies should be explored
Thresholds should be defined ‘a priori’
- Define ‘clinically-important difference’ (CID)
- Define willingness to pay for CID

Policies should prevent ‘loopholes’
- Special Access Program (SAP) circumvents marketing

Policies should consider pricing transparency
- How much is too much? Blockbuster?

Policies need to incorporate risk-sharing
- No cure, no pay!
- For example, payer pays based on ‘degree of certainty’ of outcomes, or ‘achievement’ of outcomes
Does rarity require special status?
What is the real cost?
accountability for reasonableness

Relevance:
- Based on “fair-minded” relevant criteria

Publicity:
- Rationale publicly accessible

Dispute Resolution:
- Opportunity to appeal

Enforcement:
- A4R framework accountability

Empowerment:
- Supported by change-facilitating strategies
- No comprehensive framework in place
- New orphan drugs are on the horizon
- The time for setting policy framework is now
- Past decisions should not lock future decisions (Gaucher’s)
- A new framework is required for this new era
Many thanks . . .

LHSC
LHRI
UWO
CIHR
CCOHTA
...our team!