Managed Entry Schemes

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What are we talking about

Managed entry agreements have been defined as

• “an arrangement between a manufacturer and payer/provider that enables coverage or reimbursement of a health technology subject to specific conditions.

• These arrangements can use a variety of mechanisms to address uncertainty about the performance of technologies or to manage the adoption of technologies in order to maximise their effective use or limit their budget impact”

Klemp et al Int J Technol Assess Health Care 2011; 27:77-83
What are we talking about?

**Regulator**
- Fast track
- Priority review
- Accelerated access
- Accelerated licensing
- Adaptive licensing
- Conditional marketing authorisation
- Provisional licensing

**Payer**
- Risk-sharing agreements
- Managed entry
- Conditional entry
- Access with evidence development / generation
- Coverage with evidence development

**Managing budget impact or financial uncertainty**

**Clarifying clinical uncertainty**

**Shorter clinical development times**

**Shorter review times**

**Managing budget impact or financial uncertainty**

**Clarifying clinical uncertainty**

**Only in research**

**Only with research**
Australia’s current approach

Managed entry agreements

Non-outcome based schemes
- Price-volume agreements
- Discounts
- Price or dose-capping schemes

Outcome based schemes
- Patient level
  - Conditional treatment rules
  - Outcome guarantees
- Population level
  - Coverage with evidence development

Vitry, Roughead, Health Policy 2014
The Australian experience to date:
Non-outcome based agreements

- 2003
  - First deed of agreement
    - Exchange of letters were in place prior to this
- 2013 Feb
  - 71 medicines with special pricing arrangements
    - Antineoplastics, 34%
    - CNS, 16%
    - Alimentary & metabolism, 10%
    - Cardiovascular, 7%
The Australian experience to date:
Outcome based agreements

• 2000
  - First continuation rules
    • Alzheimer’s medicines
• 2013 Feb
  - 28 medicines with continuation rules
    • TNF alphas
    • Tyrosine kinase inhibitors
    • Pulmonary hypertension
  - 20 also have special pricing arrangements
The Australian experience to date: Coverage with evidence development

- **2004** Bosentan listed for pulmonary hypertension
  - Conditional on
    - Establishment of a registry, only patients on medicine enrolled
    - Price reduction if mortality rate observed was higher than in original funding submission
  - Results
    - Observed mortality 11.8%; higher than the 5.2% in trial
    - However, patients older and had more advanced functional deficit than in the trial
  - Overtaken by subsequent events
    - 2008 Sitaxentan listed for same indication at 15% lower price than bosentan, thus bosentan price lowered to this

Vitry, Roughead, Health Policy 2014
The Australian experience to date: Coverage with evidence development

- **2010**: PBAC considered managed entry schemes for
  - Pazopanib; Imatinib
    - Considered inappropriate in the context of high price requested
- **2012**: PBAC recommended listing of ipilimumab
  - Subject to
    - Implementation of a mechanism to verify the anticipated overall survival benefits of ipilimumab in real world clinical practice in Australia… The sponsor would be expected to rebate the cost of difference in performance between observed versus predicted benefits of ipilimumab
- **2013**: PBAC considered two formal requests for consideration
  - Everolimus for subependymal giant cell astrocytomas
  - Rifaximin for hepatic encephalopathy
  - Both listed without requirement for evidence development
The international experience: Europe

- Survey and literature review of managed entry agreements in 18 European countries (2013)
- 75% of managed entry agreements were to address budget impact
  - 40% were price volume agreements
  - 13% restricted access
  - 6% conditional continuation
  - 5% reimbursement for non-responding patients
  - 5% discounts on doses (initial or general)
  - 29% requirement for data collection

Ferrario & Kanavos, European Medicines Information Network, 2013
The international experience: Europe: Rationale for managed entry

- Varies by country
- Italy, Portugal, Lithuania, the Czech Republic, and Belgium, focus on managing budget impact
- Sweden, the Netherlands and the UK, focus on maintaining cost-effectiveness

Ferrario & Kanavos, European Medicines Information Network, 2013
The international experience: Europe

- Similar medicines involved as in Australia
  - 37% antineoplastics
  - 15% alimentary and metabolism (includes diabetes)
  - 10% nervous system
The international experience:

Europe: Percentage of managed entry agreements among newly introduced compounds

Ferrario & Kanavos, European Medicines Information Network, 2013
The international experience: Europe

- Review suggests CED only reported in
  - Portugal (2 CED only, 8 PVA and CED)
  - Netherlands (39 hospital use medicines)
    - No outcomes reported

- France
  - Risperidone - does it help patients stay on their medicines
The international experience:
Europe

- Sweden (15)
  - Insulin detemir – frequency of hypoglycaemia, quality of life
  - Efalizumab – QoL and actual use in Sweden
  - Risperidone – QoL and actual use in Sweden
  - Pimecrolimus – effect on steroid resistant patients and actual use in Sweden
  - Inhalable Insulin – data to support economic value
  - Rimonabant – long term effects and economic value in Swedish setting
The international experience:

Europe

- Sweden (15) cont
  - Rasagaine – cost-effectiveness versus entacapone, selegilene
  - Ezetimibe, cerivistatin – study of actual use in Swedish health care system required, data on long term effects
  - Testosterone – study of actual use in Swedish health care system required
  - Lyphilisate – additional data on long term effects and new economic model
  - Varencline – long term effects
  - HPV – long term cost-effectiveness
  - Rotigone – actual use use in Swedish practice
  - Orlistat – actual use in Swedish practice
Italy has comprehensive registry monitoring.

At Dec 2011, 66 active compounds part of Italian monitoring registry scheme.

Registries appear to be predominantly monitoring eligibility (e.g., rebates for non-responders), safety, and appropriateness of use.
Challenges include identifying non-responders for oncology Management at local level Transparency Rationale for type of risk share

<table>
<thead>
<tr>
<th>Oncology medicines</th>
<th>Number of treated patients</th>
<th>Patients that have finalized the treatment (%)</th>
<th>Causes for Stopping the treatment</th>
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<tbody>
<tr>
<td>AVASTIN® (27/03/2006)</td>
<td>1967</td>
<td>481 (24.5)</td>
<td>Stopping the treatment by clinical decision</td>
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<tr>
<td>ELOXATIN® (27/03/2006)</td>
<td>2818</td>
<td>1127 (40.0)</td>
<td>683</td>
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<td>ERBITUX® (27/03/2006)</td>
<td>1711</td>
<td>714 (41.7)</td>
<td>53</td>
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<td>FASLODEX® (27/03/2006)</td>
<td>2853</td>
<td>778 (27.3)</td>
<td>4</td>
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<td>FOSCAN® (27/03/2006)</td>
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<td>4 (18.1)</td>
<td>0</td>
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<td>GLIADEL® (27/03/2006)</td>
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<td>44 (33.8)</td>
<td>27</td>
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<tr>
<td>ZEVALIN® (27/03/2006)</td>
<td>184</td>
<td>51 (27.7)</td>
<td>0</td>
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<tr>
<td>TARCEVA® (02/08/2006)</td>
<td>3338</td>
<td>1040 (31.2)</td>
<td>0</td>
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<tr>
<td>HERCEPTIN® (27/10/2006)</td>
<td>2156</td>
<td>144 (6.7)</td>
<td>0</td>
</tr>
<tr>
<td>NEXAVAR® (21/12/2006)</td>
<td>662</td>
<td>128 (19.3)</td>
<td>0</td>
</tr>
</tbody>
</table>

Espin, Rovira, Garcia, European Medicines Information Network 2011
Only in Research

- **UK**
  - Taxanes – 2000
  - Temozolomide – 2001
  - Oxaliplatin and irinotecan - 2002
  - Imatinib – 2002
  - Rituximab – 2003 – NHL
- **US**
  - Oxaliplatin, irinotecan, cetuximab and bevacizumab
The impact of managed entry: Risk sharing schemes

- Limited evaluation
- Mostly reports total dollars saved (or rebated)
- Can’t find any evaluation to suggest one type of risk share better than another
The impact of managed entry: Risk sharing schemes and time to access for oncology medicines in Italy

Time to access when authorization with or without a risk-sharing agreement (B).

The impact of managed entry: Coverage with evidence development

- Review of coverage with evidence development schemes published to May 2009
- Predominantly two types
  - Within clinical trial
    - 32: only 3 involved pharmaceuticals
  - Outcome guarantee arrangements
    - 26: 25 involved pharmaceuticals

Stafinski Pharmacoeconomics. 2010
The impact of managed entry:
Coverage with evidence development

• Of 32 cases where coverage was conditional on inclusion in a clinical study, predominantly medical devices or surgery
  - study outcomes were available for only half, despite average time periods of 5 years since decision (range 2 to 11 years).

• Of the 26 cases where coverage was linked to outcomes guarantees, predominantly pharmaceuticals,
  - only two reported study outcomes, despite time periods of up to 15 years
  - one with outcomes found all guarantee targets met, no rebates required
Conclusions

• Risk sharing schemes increasingly common, but coverage with evidence development less common
• Outcomes of coverage with evidence development reported more commonly for devices and surgery
  – Clarity of exposure status for devices and surgery may make this easier
  – Registries fit for purpose with complete capture have worked well for devices, however, they have not been device specific but procedure specific (eg joint replacement)
Conclusions

- Limited experience globally with coverage with evidence development for pharmaceuticals
  - Not many examples,
  - Registries that are single medicine focused have not been successful
Conclusions

- Challenges arising where coverage with evidence development has involved trials
  - Market changes supplanting need for evidence
  - Loss of funding before trial finishes
  - Loss of governance before trial finishes
  - Disputed results from negative trials
  - Negative results not acted upon
  - Lack of stakeholder support, backlash from professional and consumer groups
Conclusions

• While there is potential for earlier access and earlier benefit, there is also potential for greater risk of harm in cases where benefits not realised

• Active risk management plans implemented throughout the coverage with development cycle will be required