Should off-label agents be used as comparators in health technology assessments?

IP13, ISPOR 16th Annual European Congress

The Panel

Moderator:
- Jeanette Kusel, MSci PGDip, Head of Health Technology Assessment and Health Economics, Costello Medical Consulting

Panelists:
- Eldon Spackman, PhD, Centre for Health Economics, University of York
- Christin Andersson, PhD, The Dental and Pharmaceutical Benefits Agency, TLV, Sweden
- Andrew Walker, PhD, Clinical Trials Unit, Glasgow University and Scottish Medicines Consortium
What are off-label agents?

**Off-Label**
Use of an authorised medicinal product outside the terms of its marketing authorisation

- for a different (i.e. non-authorised) indication
- at a different dose or dosage frequency
- for a patient group not specified in the SPC (e.g., Children)

**Unlicensed**
Use of a medicinal product, or pharmaceutical form of a medicinal product, which has not been assessed or approved by the relevant authorities

- preparing a suspension from tablets
- preparing a topical product from an oral preparation
- opening a packaged product and transferring contents into syringes

Why are they used as comparators?

Does it follow sound health economic practice?

HTA agencies should compare to what is actually being displaced by a new medicine

The question is whether the additional benefits of a new medicine over current practice are worth the additional cost

Is it all due to the money? OR
Are off-label agents being used as comparators?

Example of NICE
Figure: NICE Technology Appraisals 2008-2012

Kusel J. Presentation at ISPOR 15th Annual European Congress 2012; Kusel J. Poster at HTAi Congress 2013

Questions posed to the panellists

1. What criteria should off-label use fulfil for it to be considered a valid comparator?
   a) What level of evidence of use in clinical practice is required?
   b) What level of evidence on safety and efficacy of the off-label comparator is required?
   c) Should off-label use be distinguished from unlicensed use?

2. What risks should be evaluated when considering the use of an off-label comparator?

3. To conclude, should off-label comparators be used?
Should off-label agents be used as comparators in health technology assessments?

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Eldon Spackman, PhD
Centre for Health Economics,
University of York

Conclusions

• The principle is that all relevant comparators should be included
• Pragmatically some issues
  – May depend on HTA remit
  – Methods for evaluating evidence and incorporating uncertainty
  – HTA may be willing to accept some risk
• Market failure of regulatory framework
  – Allow licensing by non-patent holders
Market Failure

- NHS may benefit from treatment
  - Willing to undergo evidence collection to determine safety and efficacy
- A manufacturer selling that treatment
  - Insufficient incentive to undertake licensing
  - Inverse incentive to undertake licensing
- Solutions
  - Allow non-patent holders to submit for licensing
  - Use other mechanisms to encourage investment

Eylea versus Lucentis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LE</th>
<th>QALYs</th>
<th>Total Cost</th>
<th>Net Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lucentis</td>
<td>11.994</td>
<td>7.758</td>
<td>£28,615</td>
<td>6.327</td>
</tr>
<tr>
<td>Eylea</td>
<td>11.995</td>
<td>7.767</td>
<td>£25,009</td>
<td>6.517</td>
</tr>
</tbody>
</table>

Benefits versus ...

• Per patient net benefit of including off-label comparator

\[ 6.995 - 6.517 = 0.478 \]

• NB>Risk

\[ 0.478 > \text{Risk} \]

Risks

• New liability
• Missed safety issue (because EMEA is better than HTA?)
  – Depends on type of off-label

\[ \text{Risk} = \text{Loss of 12 years with a chance of 5/100} \]

\[ \text{Risk} = \text{Loss of eye sight (HRQoL = 0.48) for 12 years with a chance of 8/100} \]
6.2.1 The Committee has to make judgements on the appropriateness and relevance of comparator technologies because this is crucial to the consideration of the clinical and cost-effectiveness evidence.

6.2.2 When selecting the most appropriate comparator(s), the Committee will consider:

- established NHS practice in England
- the natural history of the condition without suitable treatment
- existing NICE guidance
- cost effectiveness
- the licensing status of the comparator.

6.2.3 The Committee will normally be guided by established practice in the NHS when identifying the appropriate comparator(s). When the assessment suggests that an established practice may not be considered a good use of NHS resources relative to another available treatment, the Committee will decide whether to include it as an appropriate comparator in the appraisal, after reviewing an incremental cost-effectiveness analysis. The Committee's overall decision on whether it is a valid comparator will be guided by whether it is recommended in other extant NICE guidance, and/or whether its use is so embedded in clinical practice that its use will continue unless and until it is replaced by a new technology. The Committee will also take into account the uncertainty associated with the estimates of clinical and cost effectiveness, and whether the new technology under appraisal could provide a cost-saving alternative.

6.2.4 The Appraisal Committee can consider as comparators technologies that do not have a marketing authorisation (for CE mark for medical devices) for the indication defined in the scope when they are considered to be part of established clinical practice for the indication in the NHS. Long-standing treatments often lack a sponsor to support the licensing process. Specifically when considering an 'unlicensed' medicine, the Appraisal Committee will have due regard for the extent and quality of evidence, particularly for safety and efficacy, for the unlicensed use.

Principle versus Pragmatism

• Inclusion in analysis separate from inclusion in the decision
• Analysis
  – Quantify the uncertainty
  – Value of additional evidence collection
• Decision
  – May or may not improve the health system
  – Remit might have to change to meet principles

Should off-label agents be used as comparators in health technology assessments?

IP13, ISPOR 16th Annual European Congress
Christin Andersson, PhD
The Dental and Pharmaceutical Benefits Agency, TLV, Sweden
Disclaimer

• The content of the presentations reflects the personal view of the presenter and not the view of TLV (if not specified)

Background

• The Dental and Pharmaceutical Benefits Agency, TLV, is a central government agency whose remit is to determine whether a pharmaceutical product or dental care procedure shall be subsidized by the state.

• We regularly review the reimbursement status of medicines to see if they should remain in the reimbursement system or not.

• We perform health technology assessment of products used in the clinic (medicines and medtech products)
  – This project will end and be evaluated during 2014

• We also contribute to quality service and accessibility of pharmacies
The ideal case

• When determining whether the medicine should be eligible for reimbursement status, TLV make the assessment comparing with the most relevant treatment.

• What do TLV mean by relevant?
  • The comparator should be the most cost effective alternative – provided that it is used
  • It could be
    • Another medicine
    • Other treatment
    • No treatment

• Ideally, the comparator should be
  • within the reimbursement system
  • approved for the same indication
  • used and prescribed (in Sweden)

When could off-labels be used?

- Support from Medical Product Agency (MPA) or EMEA
- Clinical experience
- Scientific support
- Similar medical indications

Important to value similarities and differences in each individual case
Level of scientific evidence

- The use of the comparator has to be scientifically supported
- Scientific support need to be available, for example:
  - conclusive published studies
  - HTA reports
  - systematic reviews of use
- Clinical experience that support the use
- Other factors
  - Relation/similarity of chemical compounds (chemically, pharmacological)
  - Approval in other countries (NICE, SMC)
  - Swedish or international guidelines
  - Information from evaluation at other reimbursement agencies

Lucentis

- Evaluated in 2012 (no decision)
- MPA: not enough safety data to be able to compare Lucentis and Avastin.
- Laser could also have been considered as comparator

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Lucentis</th>
<th>No treatment</th>
<th>Ozurdex</th>
<th>Avastin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism /Active compound</td>
<td>VEGF blocker /ranibizumab</td>
<td>-</td>
<td>Dexamethasone/ intravitreal implant</td>
<td>VEGF-blocker/ bevacizumab</td>
</tr>
<tr>
<td>Approved indication</td>
<td>Diabetic macular edema (DME) Central/Branch Retinal Vein Occlusion (CRVO, BRVO)</td>
<td>CRVO, BRVO (Cost effectiveness not evaluated)</td>
<td>Colorectal. Lung and Kidney cancer. Glioblastoma</td>
<td></td>
</tr>
</tbody>
</table>
Premalex

- Approved for reimbursement (2012)
- Premalex - first drug approved for treatment of PMDS in Sweden
- No guidelines and no recommendations from MPA
- One swedish county recommended use of generic compound instead of Premalex at time for decision

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Premalex</th>
<th>No treatment</th>
<th>Cipralex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism /Active compound</td>
<td>5HT antagonist /escitalopram</td>
<td>-</td>
<td>5HT antagonist /escitalopram</td>
</tr>
<tr>
<td>Approved indication</td>
<td>Premenstrual dysphoric syndrom (PMDS)</td>
<td>Indication: Panic syndrome, social phobia, general anxiety</td>
<td></td>
</tr>
</tbody>
</table>

Using off label agents as comparators

- Advantages
  - Always using the most cost effective alternative as comparator
  - Comparing with the medicine actually being used
  - Potential for including medicines with approved indication in the reimbursement system (at approval)

- Disadvantages
  - Patient safety- the clinical documentation only available for the specific indication
  - Indirect "approval" of the off label agent (at rejection)
Should off labels be used?

- In cases when the most relevant comparator is a medical treatment alternative that is widely used but lacks approval for the specific medical indication or is a cost effective treatment alternative outside the reimbursement system, that comparator could be used.

- Patient safety should always be prioritised.

- Impossible to predict exact criteria to be fulfilled (i.e. exactly what studies)

- It should still be an individual evaluation for each specific case

Acknowledgements

- Jonas Lindblom
- Lisa Landerholm
- Marianne Aufrecht-Gustafsson
- Rune Dahlqvist
- Stefan Odeberg
One rule for us and another for you? Or sensible pragmatism?

Dr Andrew Walker
Clinical Trials Unit, Glasgow University
and
Scottish Medicines Consortium

The HTA thought process

• We are different to licensing – we talk about added long-term value compared to treatments currently used
• Therefore using the wrong comparator undermines the whole submission and likely leads to not recommended guidance
• We do not have a pre-conceived view of current treatment for all diseases
• Therefore we ask Scottish doctors, pharmacists and other prescribers
• For each submission (licensed indication)
  • Why would the fact current treatment is off-label stop us?
How we do it

• No scoping meetings at SMC
• ‘Experts’ = clinicians who treat relevant patients
• Recruited via Area Drug & Therapeutics Committees
• Usually ask around 10, expect 5-6 replies
• Asked how they manage patients who match the license just now
• Variability in answers, looking for majority view
• Can be asked questions to clarify or test a viewpoint put forward in the submission

Early, contentious off-label examples

• Pimecrolimus for atopic dermatitis

• Pregabalin for neuropathic pain

• Companies contended cheap, generic comparators were not licensed and therefore invalid
More recent off-label examples

- Dabigatran and NOACs – compared to warfarin, aspirin, and there was no issue about license (I still don’t know if they have one!)
- Botox in migraine
- Linaclotide in IBS
- Both ‘forced’ into comparison with ‘off-label’ medicines because of need to seek a niche position

Bevacizumab for eye disease

- Not reviewed – only review licensed products
- Only mention is in guidance for aflibercept
- “Bevacizumab is unlicensed and its ‘off-label’ status should be clearly stated prior to its use in patients. There are no long-term results on safety and effectiveness of intravitreal bevacizumab.” (under “Additional Information” on page 8 of 11)
- Not listed in cost of relevant comparators table, not mentioned in feedback from experts, not required as a comparator in health economics (or clinical effectiveness)
Is ‘unlicensed’ a ‘modifier’?

- Example of belimumab in SLE
- ‘Off-label’ rituximab is used at present
- SMC ‘modifier’: alternative to unlicensed use ... so can belimumab use this as an argument?

- SMC decided not and clarified ‘modifier’:
  - “Emergence of a licensed medicine as an alternative to an unlicensed product that is established in clinical practice in NHS Scotland as the only therapeutic option for a specific indication. Some possible examples include caffeine injection for the treatment of apnoea of prematurity and betaine anhydrous for the adjunctive treatment of homocystinuria.”

And back to bevacizumab ...

- In its licensed indication for ovarian cancer, the stated dose is X
- In practice, its likely use is at a dose of < X
- When the dose is X, the cost per QALY is high, but at dose < X the cost per QALY could be regarded as ‘reasonable’
- SMC would have to grant approval for use of bevacizumab at a dose that was not licensed ...
- ... and it did not feel able to do so
- The medicine was not recommended in this indication, much to the disappointment of Scottish oncologists
Other ‘grey area’ comparisons

- Comparator used but not recommended in HTA
  - Example: lapatinib in breast cancer
- Comparator ineffective(!)
  - Example: dasatinib in CML
- Comparator used in sub-optimal dose and if used optimally, new medicine would not be cost-effective
  - Example: ivabradine in chronic heart failure

What should a company do?

- Fieldwork establishes current treatment in Scotland is off-label use of medicine
- Might consider avoiding it – choose a niche, but do you have clinical evidence for that niche?
- Otherwise: embrace it and submit the best evidence you can, even if you feel it is weak
- Estimate of effectiveness could come from a UK-based audit of current practice or even expert opinion
- No form of evidence is too weak (except making it up!), we consult our clinical experts and look for sensitivity analysis
My answers to Jeanette’s questions

• Off-label use is a valid comparator if clinical experts tell us it is widely used – no evidence on efficacy and safety is required to justify this
• Unlicensed and off-label are different in our eyes
• If SMC says no, this leaves the situation in terms of off-label use to expert judgement, so no risk (in our eyes)
• SMC guidance would not be credible without off-labels being included so they must be used