First Plenary Session
THE PATIENT AND HEALTH TECHNOLOGY ASSESSMENT: CHALLENGES AND OPPORTUNITIES

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Health Technology Assessment of the new Cystic Fibrosis Drug

Michael Barry

4th November 2013
For discussion

• Background: Drug expenditure, pharmacoeconomic assessment process
• The patient and HTA in Ireland – the Ipilimumab controversy
• Ivacaftor: Evidence and submitted economic evaluation
• The price v ICER relationship for ivacaftor
• Areas of concern to the HTA review group
• Pharmacokinetics of ivacaftor – economic implications
• NCPE recommendation
• Comments/observations on recent HTAs

Drug expenditure in Ireland

Expenditure on medicines in Ireland
(Community Drugs Schemes 1991 - 2013)
Pharmacoeconomic assessment process

Pharmaceutical Company

HSE - CPU → NCPE

National Centre for Pharmacoeconomics (NCPE)

Health Service Executive – Corporate Pharmaceutical Unit (HSE-CPU)

RAPID REVIEW

(www.ncpe.ie)

Pharmacoeconomic assessment process

Pharmaceutical Company

HSE - CPU → NCPE

HTA report

90 days

Pharmaceutical Company

Principles and Process for the Reimbursement of New Medicines in Ireland – Annex I (IPHA Agreement 2012)
Cost-effectiveness threshold – IPHA 2012

The QALY threshold to be used in the HTA process is € 45,000

The patient and Health Technology Assessment

Ipilimumab
‘Ippli’

“We believe the Company has failed to demonstrate the cost-effectiveness of ipilimumab for the treatment of advanced melanoma in adult patients who received prior therapy. We cannot recommend reimbursement at the submitted price”.

Price: € 85,000/patient
Budget impact: € 4,800,000 - € 7,400,000 per annum
Δ median overall survival = 3.6 months
Basecase ICER: €147,899/QALY or €92,443/LYG

September 2011
The Ippi controversy!

Final ICER ~ € 116,000/QALY

“First Ever Drug to Treat ‘Celtic Gene’ In Cystic Fibrosis Sufferers”

Ipilimumab (Yervoy)  Ivacaftor (Kalydeco)
Outcomes: 1. $\Delta$ from baseline predicted FEV1% was 10.6% greater for ivacaftor at 24 weeks
2. patients were 55% less likely to have a pulmonary exacerbation over 48 weeks
3. the treatment group scored 8.6 points higher on the respiratory symptoms domain of the Cystic Fibrosis Questionnaire at week 48 (a 100 point scale).
4. weight gain of 2.7 kg over placebo group by 48 weeks

Cost: priced over €234,000 per patient per year

Submitted economic evaluation

The objective was to assess the cost-effectiveness of ivacaftor as an adjunct treatment for CF in patients aged 6 years and older who have a G551D mutation in the CFTR gene.

A patient level simulation was constructed to estimate clinical outcomes and costs in a population of patients with CF who have a G551D mutation.

The perspective was that of the healthcare payer (Health Service Executive).

Cost-effectiveness outcomes were estimated over a lifetime horizon with costs and benefits discounted at 4%.

The methodology involved the fitting of Irish survival curves to a Weibull function, the production of a hazard for mortality function and determining how this hazard is changed when risk factors are improved.
Submitted economic evaluation

The FEV1 % predicted, weight for age z-scores and exacerbations were considered responsive to ivacaftor.

The modelled survival benefit when ivacaftor was added to standard of care was estimated at a median of 29.2 years (remaining lifespan increased from 18.5 years to 47.7 years from baseline). The main driver of the estimated effect of ivacaftor on survival was the difference in % predicted FEV1 progression between the treatment groups.

The basecase scenario assumed the % predicted FEV1 remained stable over time whereas it declined for patients on placebo.

Basecase ICER = €449,035/QALY

Price vs ICER relationship

€449,000/QALY

ICER €/QALY

€45,000/QALY

0 €50,000 €100,000 €150,000 €200,000 €250,000

€22,000/patient/annum at the CE threshold of €45,000/QALY

Ivacaftor price/patient/annum €234,000 ‘asking price’
Price vs ICER relationship

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<tr>
<th>€/QALY</th>
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Ivacaftor price/patient/annum

Price reduction ??

€22,000/patient/annum at the CE threshold of €45,000/QALY

€234,000 "asking price"
Submitted economic evaluation – areas of concern

The absence of long term data in relation to the beneficial effects of ivacaftor on the percent predicted FEV1, pulmonary exacerbations and overall survival. Changes to the assumptions surrounding the % predicted FEV1 impacted considerably on the ICER.

An alternative scenario (conservative) assumed the FEV1 slope over time was set identical to the standard of care and the only benefit from ivacaftor was the immediate increase in % predicted FEV1.

Alternative scenario ICER = € 855,437/QALY

Submitted economic evaluation – areas of concern

The manufacturer submission confirmed that “some patients showed little to no improvement in FEV1 and still others showed decline”. Minimal response was defined as patients with < 5 point absolute change from baseline in % predicted FEV1. This occurred in approx 26% of patients through week 48 of the STRIVE study and 38% in ENVISION.

Interim results from the PERSIST trial indicated that 45% of patients continuing on ivacaftor had pulmonary exacerbations.

The review group felt that uncertainty was not adequately accounted for with the provision of a limited one way sensitivity analysis and the absence of a probabilistic sensitivity analysis.

Failure of the manufacturer to demonstrate cost-effectiveness of ivacaftor and the significant budget impact in the region of € 28 million per annum.
Ivacaftor is extensively metabolised in humans, primarily by hepatic cytochrome P450 3A4. Major metabolites include M1 (1/6 potency of ivacaftor) and M6 (pharmacologically inactive).

**Twice weekly vs twice daily?**
Cost-effectiveness of Ivacaftor (Kalydeco) for the treatment of cystic fibrosis in patients age 6 years and older who have the G551D mutation

Basecase ICER: € 449,035/QALY or € 443,825/LYG
Price: € 234,804/patient
Budget impact: € 28,000,000 per annum

HTA conclusion

“In view of the very high drug acquisition cost, the significant budget impact, the absence of long term clinical data and the fact that the company has failed to demonstrate the cost-effectiveness of ivacaftor we cannot recommend reimbursement of ivacaftor at the submitted price of € 234,804 per patient per annum”.

“A mechanism such as a performance based risk sharing scheme and/or a significant reduction in price could facilitate access to ivacaftor treatment for cystic fibrosis patients with the G551D CFTR mutation”.

NCPE January 2013
Recent ICERs

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Opportunity Cost!

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The Cystic Fibrosis Association of Ireland played a very important role during the Ivacaftor HTA process particularly during the time between the NCPE recommendation and the reimbursement decision.

It is evident that simply concentrating on HTA methodological expertise is necessary but not sufficient for the successful conduct of the HTA process. There is little doubt that patients have to be involved.

Patient involvement will probably be influenced by characteristics of the HTA process that exists e.g. timelines around the process (90 days in Ireland).

Given that patients should be involved there are many questions: How? At what stage? In what way? etc

As a HTA Agency we note the increasing frequency of submissions of high cost products with incremental cost-effectiveness ratios (ICERs) well above the cost-effectiveness threshold, particularly in the field of oncology and rare diseases.

Is this sustainable?

Expectations of stakeholders (Pharmaceutical Industry, Clinicians, Patients) continues to increase despite a finite (and occasionally reducing) healthcare budget. Stakeholders should be aware that the reimbursement of products with very high ICERs comes with an opportunity cost.
Comments/observations

In the era of molecular medicine some appear to believe that ‘personalised medicines’ are always “innovative” and automatically qualify for a very high reimbursement price!

Clinicians involved in the care of patients with cystic fibrosis played a very constructive role at all times during the Ivacaftor HTA process.

Occasionally clinicians welcome the introduction of new high cost products with modest healthcare benefits (or occasionally negligible benefits) using terminology such as “phenomenal” or “spectacular” etc - this is unhelpful.

Delivering affordable healthcare

“The cancer profession and industry should take responsibility and not accept a substandard evidence base and an ethos of very small benefit at whatever cost: rather, we need delivery of fair prices and real value from new technologies”

“fair prices and real value”

Thank you