# Economic Evaluation of iloprost, epoprostenol and treprostinil for the treatment of pulmonary arterial hypertension

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## Objectives

Pulmonary arterial hypertension (PAH) is a chronic orphan disease characterised by an elevated mean pulmonary artery pressure[1,2]. Patients with PAH experience shortness of breath with effort, limited exercise capacity, edema and syncope and are threatened by progressive right heart failure and premature death[3]. Also quality of life (QoL) is considerably impaired in this kind of patients[4].
International pharmacoeconomic literature on PAH is scarce[5-9] and there is no evidence under the Spanish setting. The objective of this study is to analyze the efficiency of three existing alternative treatments (inhaled iloprost (ILO), intravenous epoprostenol (EPO) and subcutaneous treprostinil (TRE)) for patients suffering from pulmonary arterial hypertension iniciating therapy with a prostanoid in Spain.

## Methods

A Markov model was built to simulate a PAH patient cohort in functional class III of the New York Heart Association (NYHA). Data sources were: 1) literature review, 2) costs databases and 3) expert opinion. The model had four health states, those of the functional classes, plus death (Figure 1).

No comparative studies between EPO, ILO and TRE were found, so transition probabilities were calculated using the same methodology as that of other cost-effectiveness evaluations[5] based on pivotal clinical trials of each prostanoid[10-12]. For a more reliable adjustment of the probabilities of transition to death, data from a meta-analysis were applied[13]. Transition probabilities were assumed to be time independent (Table 1).

At the base case, treatment changes were allowed when patients worsened from class III to IV in proportions agreed by the experts' panel. Time horizon was three years and transition cycles were of 12 weeks.

It was assumed that underlying oral therapy, in case of its existence, was equally distributed among the three patient groups.

Perspective was that of the National Health System (NHS) in Spain. Costs were expressed in €2009. Costs and effects were discounted at a 3% rate following Spanish recommendations. Drug prices, which account for most of the economical burden, are shown in Table 2.

Quality-adjusted life years (QALY) were calculated by multiplying life years gained (LYG) by utility values estimated from Keogh et al.[15] in the same way as in other studies[8,16]. Taking into account that Keogh study was developed with bosentan patients, an alternative set of utilities provided by the expert panel was tested in a sensitivity analysis (Table 3).

Both, deterministic and probabilistic sensitivity analyses were performed to check for robustness of results.

## Results

At three years, results of initiating prostanoid therapy with ILO, EPO and TRE were, respectively (Table 4).

Resulting conclusions from the calculation of incremental cost-effectiveness and cost-utility ratios are shown in Table 5.

The evolution of mortality figures from model simulation shows that, at three years, epoprostenol is the treatment that better keeps mortality under control. These figures were taken as a proxy to validate model simulation (Figure 2).

Probabilistic sensitivity analyses confirm robustness of results (Figure 3).

## Conclusions

Initiating prostanoid therapy in class III PAH patients with intravenous epoprostenol is more efficacious than the alternatives. At a three-year time horizon, inhaled iloprost shows to be by far the less costly alternative for the NHS in Spain.

The incremental cost-utility ratio of epoprostenol versus iloprost and treprostinil is much above the commonly acceptable threshold in Spain[17], so it is not a cost-effective option from the NHS perspective. Iloprost is a dominant treatment when compared to treprostinil.

Figure 1. Markov diagram

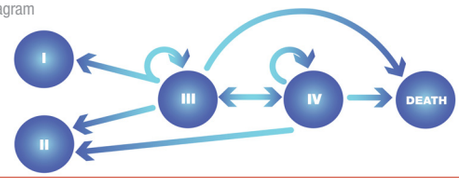



Table 1. Estimated transition probabilities for prostanoids

| | FROM CLASS: Epoprostenol III | Epoprostenol IV | Iloprost III | Iloprost IV | Treprostinil III | Treprostinil IV |
|---|---|---|---|---|---|---|
| TO CLASS I | 0.013 | 0 | 0.010 | 0 | 0.099 | 0 |
| II | 0.321 | 0.015 | 0.236 | 0.011 | 0.218 | 0.010 |
| III | 0.565 | 0.356 | 0.640 | 0.262 | 0.656 | 0.242 |
| IV | 0.088 | 0.615 | 0.099 | 0.710 | 0.102 | 0.731 |
| Death | 0.013 | 0.014 | 0.015 | 0.016 | 0.015 | 0.017 |

Table 2. Drug costs

| Treatment alternative | Epoprostenol | Iloprost | Treprostinil |
|---|---|---|---|
| Cost of 12 weeks treatment | 39.729€ | 8.974€ | 33.294€ [14] |

Table 3. Utility values

| CLASS | Utility values[15] (95% CI) | Alternative utility values |
|---|---|---|
| I | 0.73 (0.64-0.82) | 0.73 |
| II | 0.67 (0.57-0.77) | 0.63 |
| III | 0.60 (0.50-0.70) | 0.51 |
| IV | 0.52 (0.43-0.61) | 0.43 |

Table 4. Results at a three-year time horizon

| Treatment alternative | Epoprostenol | Iloprost | Treprostinil |
|---|---|---|---|
| Total cost of treatment (€) | 430,271 | 143,092 | 360,387 |
| Efficacy (LYG)) | 2.729 | 2.695 | 2.690 |
| Utility (QALY) | 1.780 | 1.737 | 1.728 |
| Mean cost/LYG (€) | 157,678 | 53,092 | 133,997 |
| Mean cost/QALY (€) | 241,667 | 82,376 | 208,595 |

Table 5. Cost-effectiveness relationships conclusion

| | Iloprost | Treprostinil |
|---|---|---|
| Epoprostenol vs. | Not cost-effective | Not cost-effective |
| Iloprost vs. | | Dominant |

Figure 2. Mortality evolution within a three-year time horizon

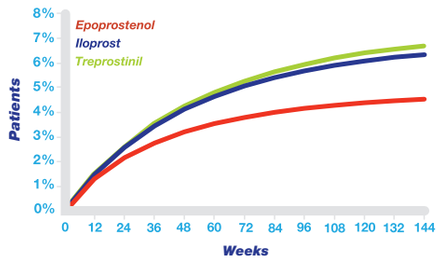
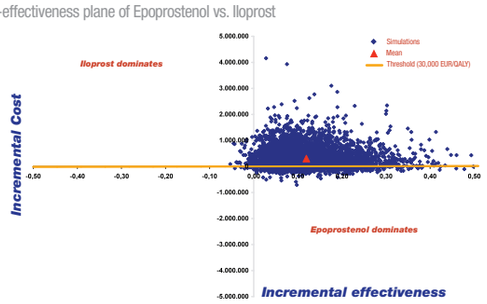



Figure 3. Cost-effectiveness plane of Epoprostenol vs. Iloprost

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*This study was funded*
Bayer HealthCare
Bayer Schering Pharma

ISPOR 13th Annual European Congress
6-9 November 2010, Prague, Czech Republic