How Does the Scottish Medicines Consortium Assess the Value of Orphan and Ultra-Orphan Drugs?

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BACKGROUND

Health Technology Assessment of Orphan Drugs

- The economic evaluation of treatments for orphan and ultra-orphan diseases is a rapidly evolving policy area. Currently, health technology assessment (HTA) policy with regards to orphan and ultra-orphan diseases varies widely across countries.
- The definitions used for orphan and ultra-orphan diseases differ between countries.[1,2] This will require consideration when submitting to a number of international HTA organisations.
- Increasing pressure on health care budgets necessitates that all new health care technologies demonstrate sufficient value for money in the clinical benefits that they offer to patients. This is equally true of orphan drugs.[3]
- However, new and innovative drugs for such diseases rarely achieve standard cost-effectiveness thresholds due to high acquisition costs. High research and development costs must be recouped over a far smaller patient population, leading to higher costs per patient.[4]
- Furthermore, limited information on natural history, clinical efficacy, and safety data at product launch can provide challenges and uncertainty with regard to accurately estimating the cost-effectiveness of an orphan or ultra-orphan product.

Scottish Medicines Consortium

- The Scottish Medicines Consortium (SMC) adopts the definition of orphan drugs used by the European Medicines Agency. A drug is deemed an orphan medicine if it is licensed to treat life-threatening diseases affecting fewer than 5 in 10,000 people in the European Union.[2] A new medicine fulfilling these criteria can be submitted to the SMC under the orphan drugs process.
  - A manufacturer will state in its submission that a product is to be assessed under the orphan or ultra-orphan process and will provide supporting evidence.
  - The product will then be evaluated under the normal process by the New Drugs Committee (NDC). If the product is not recommended, a pharmaceutical company may request that a Patient and Clinical Engagement (PACE) meeting be convened.
  - PACE meetings are designed as an assessment process to broaden the decision-making framework beyond what would be considered in a standard assessment process to look at additional criteria beyond cost-effectiveness.[5]
  - If a medicine is not recommended by the NDC, a company is also able to offer a Patient Access Scheme (PAS) to improve the cost-effectiveness of its product.
- Following appraisal of the manufacturer's submission document, the SMC can publish the following recommendations:
  - Accept
  - Accept for restricted use
  - Not recommend
- The SMC has no stated threshold for orphan products. In England and Wales, the National Institute for Health and Care Excellence (NICE) recently proposed guidelines for highly specialised technology appraisal for very rare conditions in which a threshold of up to £300,000 per quality-adjusted life-year (QALY) gained would be employed rather than the standard £20,000-£30,000 per QALY gained used for non-orphan treatments.[6]

OBJECTIVE

- This study investigates whether the SMC uses an implicit cost-effectiveness threshold when assessing the value of orphan drugs.
- Additionally, PACE criteria cited in orphan and ultra-orphan appraisals are evaluated to determine the criteria of most relevance to decision makers. Furthermore, an investigation is made into which criteria are commonly cited by the PACE groups.

METHODS

- The SMC website was searched from January 2015 to May 2017 for submissions made under the orphan or ultra-orphan submission processes.
- Data were extracted regarding the submission process, SMC recommendations, use of a PAS, and the incremental cost-effectiveness ratio (ICER). If a with-PAS ICER was unavailable, the without-PAS ICER was extracted.
- PACE criteria for each submission were reviewed to assess additional aspects of value considered by the SMC.

RESULTS

- The review identified 48 submissions under the orphan and ultra-orphan processes.
- During the period assessed, the SMC accepted 40% of full submissions under the orphan and ultra-orphan HTA processes. A further 25% of submissions were accepted for restricted use (Figure 1).
- The SMC routinely accepts technologies for orphan drugs with ICER values around £50,000 per QALY gained.
- There were 15 submissions either accepted or accepted for restricted use with ICERs above £30,000 per QALY. The highest ICER for an accepted product was £52,201 per QALY gained (Table 1).
- The SMC rejects submissions with substantial uncertainty surrounding the ICER even when the ICER is substantially below £50,000 per QALY (Table 2).
- Almost all submissions made under the orphan and ultra-orphan submission processes requested that a PACE meeting be convened. Other aspects of value commonly cited by the PACE group included unmet need in the disease area, convenience of drug administration compared with current treatment, age of the population most affected by the disease, and whether the treatment may facilitate a return to work.
- The review also highlighted the challenges associated with achieving traditional cost-effectiveness thresholds in some orphan and ultra-orphan treatments. The highest ICER value submitted to the SMC during the period assessed was £829,870 per QALY gained.

Table 1. ICERs and PACE Criteria for Selected Orphan Products Recommended by the SMC

Drug Name	Base Case ICER[a] (£ per QALY)	PACE Criteria
Blinatumomab	£52,201	• High symptom burden • Young patient population • Few alternative treatment options • High remission rates in this difficult-to-treat population • Convenience of administration
Ceritinib	£50,908	• Has a large impact on quality of life • Unmet need in third-line options for these patients • Significant improvement in overall survival at the end of life • Manageable side effects
Crizotinib	£48,355	• High symptom burden • Favourable adverse event profile • Convenience of administration • Young patient population
Lenvatinib	£49,525	• Condition is associated with significant reduction in life expectancy • Limited current treatment options • Convenience of administration • Manageable side effects
Ruxolitinib	£49,774	• High symptom burden • No current treatments effectively address the symptoms • Symptoms may be reduced such that come patients can return to work • Reduced dependency on carers
Trifluridine	£49,225	• Very poor survival rate among patients diagnosed with this disease • Limited treatment options in final stages of disease • Tolerable adverse event profile

[a] All ICERs presented here are inclusive of a PAS.

Table 2. ICERs and Submission Limitations for Selected Orphan Products Not Recommended by the SMC

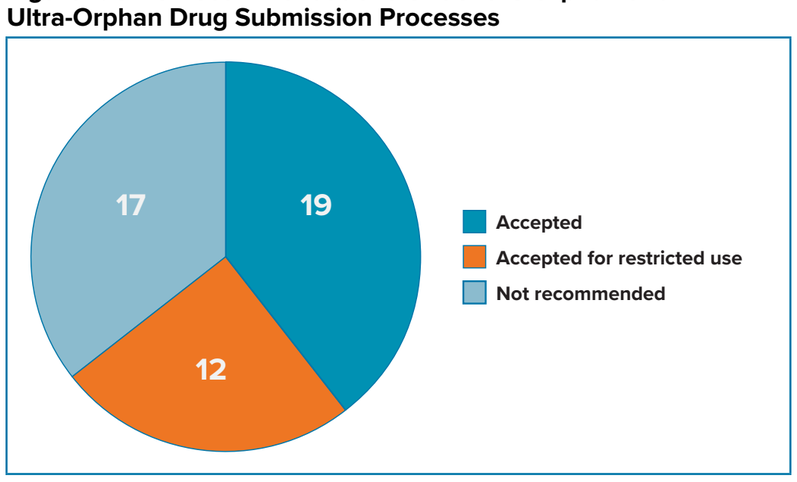
Drug Name	Base Case ICER[a] (£ per QALY)	Limitations
Enzalutamide	£31,524	• ICER was very sensitive to overall survival extrapolation • Assumption that utility post-progression was the same as pre-progression
Hydrocortisone modified release	£26,140	• Uncertainty surrounding quality-of-life estimates • Lack of robust clinical data linking short term and long-term outcomes
Nivolumab	£24,483	• Lack of long-term data to support assumptions made in the model • Concerns raised surrounding robustness of indirect comparisons • Not generalizable to population that had received first-line therapy
Pembrolizumab	£43,234	• ICER was very sensitive to overall survival extrapolation • Overall survival data confounded by crossover from control arm of clinical trial • Model based on time to death rather than disease progression
Pertuzumab	£34,100	• Immaturity of trial data leading to uncertainty of long-term extrapolation • Uncertainty surrounding length of treatment effect • Utility values were taken from literature and not trial data

[a] All ICERs presented here are inclusive of a PAS.

DISCUSSION

- The review was somewhat complicated by the fact that, due to information being commercial in confidence, several submissions did not report the without-PAS ICER. Thus it was impossible to know with certainty the ICER that was considered by the SMC in its final decision. Several products with high ICERs were deemed cost-effective when the PAS was considered. These discounts were not published.
- PAS discounts are being used as a value-based pricing mechanism to achieve ICER values around £50,000 per QALY to make treatments acceptable for submissions to the SMC.
- In cases with high ICER values, PACE criteria are considered by the SMC. It is difficult to assess with certainty which of these are considered most valuable by the SMC decision-making committee. Discussion on the relevance of PACE criteria to the final appraisal decision is not included in the published SMC advice document.
- Submissions with low ICER values may not be recommended by the SMC on methodological grounds. This underlines the data challenges and uncertainty often present in orphan and ultra-orphan submissions.
- Key limitations included uncertainty surrounding long-term extrapolation of clinical trial data and a lack of robust utility estimates.

Figure 1. SMC Recommendations Under the Orphan and Ultra-Orphan Drug Submission Processes



Searches were performed between January and May 2017, and a total of 48 submissions were identified.

CONCLUSIONS

- The SMC appears to employ a cost-effectiveness threshold of £50,000 per QALY when assessing whether an orphan or ultra-orphan medicine should be offered to patients in Scotland.
- NICE's proposed threshold of between £100,000 and £300,000 per QALY for orphan diseases may lead to disparities in access to treatments between patients in Scotland and patients in the rest of the United Kingdom.
- The SMC incorporates PACE criteria considering additional aspects of value beyond cost-effectiveness. Although these criteria are included in the assessment reports produced by the SMC, it is difficult to deduce which of these criteria are deemed most important in the appraisal decision.
- Manufacturers may consider strategies including convening a Delphi panel to advise on modelling parameter inputs or commissioning a utility study to reduce the uncertainty surrounding the results of the model and strengthen the evidence presented to the HTA authority.
- Increased transparency of SMC requirements for reimbursement of orphan drugs would be welcomed by Scottish patient groups and manufacturers.

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Presented at: ISPOR 20th Annual European Congress, November 4-8, 2017, Glasgow, Scotland